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Total synthesis of the *Z*-isomers of nonenolide and desmethyl nonenolide

Gowravaram Sabitha *, P. Padmaja, K. Sudhakar, J. S. Yadav

Organic Division-I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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ABSTRACT

RCM and Yamaguchi esterification reactions were used as the key steps for the stereoselective total synthesis of *Z*-isomers of nonenolide and desmethyl nonenolide.

1. Introduction

The ascomycetous genus *Cordyceps* is a rich source of biologically active secondary metabolites, such as antimalarial erythostominones,[1] antimalarial cordypyridones,[2] and antitumor sterols.[3] It has also found extensive use in food and herbal medicines in Asia. However, reports on the isolation of secondary metabolites from *Cordyceps militaris*, an enthomopathogenic fungus belonging to the class of ascomycetes, have been sparse. Cordycepin (3′-deoxyadenosine), a secondary metabolite previously isolated from *C. militaris* possesses antifungal-, antiviral-, and antitumor activities. Nonenolide **1**, a medium-sized macrolide, was recently isolated as a white solid from *C. militaris BCC* 2816, and showed antimalarial activity.[4] The structure was elucidated by spectroscopic data and X-ray crystallographic analysis. In spite of its interesting antimalarial activity, a few syntheses of **1** have been recently reported.[5] In continuation of our interest on the synthesis of bio-active lactones[6] using ring-closing metathesis (RCM) as a key step, we herein report the synthesis of *Z*-isomers **3** and **4** of nonenolide **1** and desmethyl nonenolide **2** (Fig. 1) using RCM reactions. Our strategy involves the esterification of two appropriately functionalized components under the Yamaguchi conditions, followed by the Grubb catalyst-mediated ring-closing metathesis to afford the target compounds.

Our retrosynthetic analysis is depicted in Scheme 1. *Z*-Isomers, **3** and **4** could be synthesized by the RCM reaction of **5** and **10**, respectively. These intermediates in turn could be synthesized from the fragments **6**, **7**, and **11** via the Yamaguchi esterification. The common fragment **6** for both targets, could be obtained from **9**, fragments **7** and **11** could be derived from the 4-penten-1-ol **8** and commercially available 1,4-butane diol **12**, respectively.

2. Results and discussion

The synthesis of acid component **6** began with **13** prepared from homopropargyl alcohol **9** by a literature procedure.[7] The primary hydroxyl group in **13** was oxidized with Dess–Martin periodinane[8] (DMP) to afford the corresponding aldehyde, which was oxidized to the acid **6** with $NaClO_2$ in the presence of $NaH_2PO_4{\cdot}2H_2O$ and 2-methyl-2-butene[9] in 80% yield over two steps (Scheme 2).

Simultaneously, another intermediate **7** was synthesized from chiral epoxide **14**, prepared from 4-pentene-1-ol **8** following the literature procedure.[10] The reduction of **14** with LAH in THF at rt for 2 h afforded secondary alcohol **15** in 70% yield. The secondary alcohol was protected as THP ether **16** with 2,3-dihydropyran in the presence of PTSA (cat.) in CH_2Cl_2 followed by removal of the

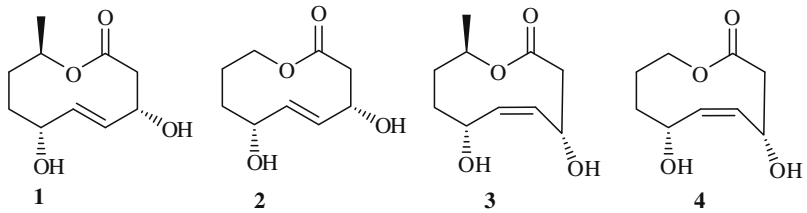

Figure 1.

* Corresponding author. Tel./fax: +91 40 27160512.
E-mail address: gowravaramsr@yahoo.com (G. Sabitha).

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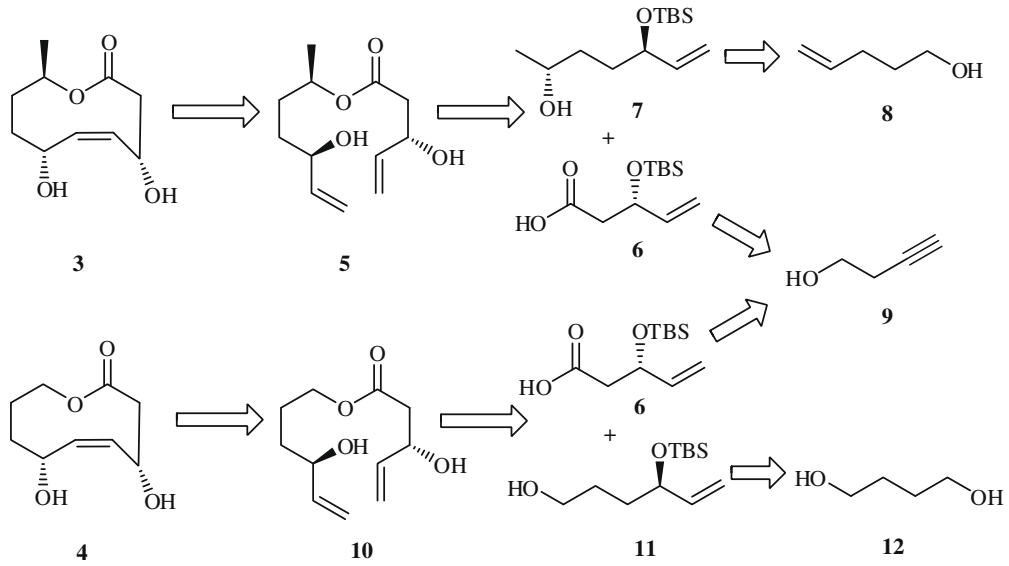
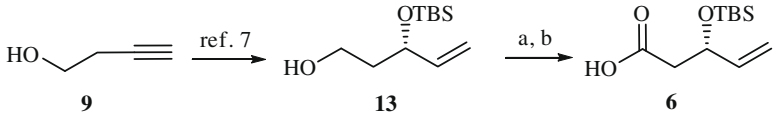


Scheme 1. Retrosynthetic analysis.



Scheme 2. Reagents and conditions: (a) DMP, CH_2Cl_2, 0 °C to rt, 1 h, 95%; (b) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, 2-methyl-2-butene, *t*-BuOH, 6 h, 70%.

benzyl group with Pd/C in EtOAc to afford **17** (85%). The primary hydroxyl was oxidized to the aldehyde under Swern conditions[11] and homologated by a two-carbon Wittig ylide, (ethoxycarbonylmethylene)triphenyl phosphorane in benzene at reflux for 3 h furnishing α,β-unsaturated ester **18** in 90% yield. Ester **18** was reduced with DIBAL-H in CH_2Cl_2 at 0 °C to allylic alcohol **19** in 85% yield. Sharpless epoxidation of allylic alcohol **19** with (−)-DET, $Ti(O^iPr)_4$, and cumene hydroperoxide in dry CH_2Cl_2 for 5 h afforded **20** (75%). The epoxy alcohol was converted into the corresponding iodide[12] **21** with iodine, Ph_3P, and imidazole for 1 h (90%), which on reductive elimination with activated Zn dust[13] in refluxing ethanol for 2 h afforded chiral allylic alcohol **22** (80%). The secondary hydroxyl was protected as the silyl ether **23** with TBDMSCl and imidazole and deprotection of the THP group[14] with solid NH_4Cl in MeOH at reflux temperature afforded the required alcohol fragment **7** (70%) (Scheme 3).

Next, we attempted to couple the two fragments in order to construct a 10-membered ring by RCM reaction. Accordingly, the Yamaguchi protocol was (DCC and DMAP)[15] explored to afford diene ester **24** in 85% yield (Scheme 4). It is important to note that the RCM reaction did not proceed when the two hydroxyl groups were protected as TBS ethers. Therefore, two TBS groups in **24** were removed using TBAF in THF to afford diol **5** and the ring-closing metathesis reaction using Grubbs' second generation catalyst[16] was performed in CH_2Cl_2 at reflux temperature for 3 h to afford the *Z*-isomer of nonenolide **3** in 70% yield. The spectroscopic data of synthetic **3** are in good agreement with those reported in the literature.

The synthesis of **11** began with the commercially available 1,4-butane diol **12** by following the known reactions. Thus, mono protection (DHP/PTSA/CH_2Cl_2/rt), Swern oxidation, and homologation by a two-carbon Wittig ylide, ester reduction, epoxidation, iodination, and reduction by zinc gave compound **30**. Next, the secondary alcohol was protected as its TBS-ether and THP deprotection to give the required fragment **11** (Scheme 5).

With two key fragments **6** and **11** in hand (Scheme 6), the next concern was to couple them by a Yamaguchi reaction to afford the diene ester **32**. The RCM reaction in **32** was not successful as was the case with **24** in Scheme 4. The two TBS groups were removed to give compound **10**. Finally, treatment of **10** with Grubbs' catalyst II in CH_2Cl_2 at reflux temperature for 3 h afforded the *Z*-isomer of desmethyl nonenolide **4** in 70% yield. The structure and stereochemistry were established by ^1H and ^{13}C NMR analysis (Scheme 6).

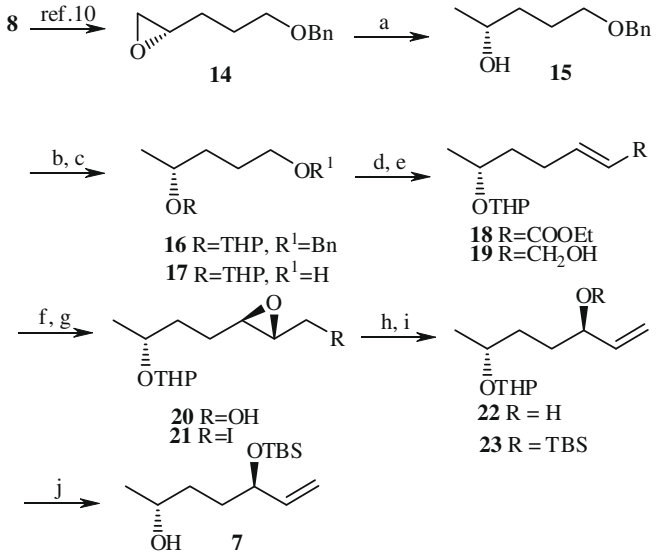
3. Conclusions

In conclusion, the total synthesis of the *Z*-isomers of nonenolide and desmethyl nonenolide has been accomplished. The highlights of the synthesis are the utilization of RCM and Yamaguchi cyclization reactions as the key steps.

4. Experimental

4.1. General

Reactions were conducted under N_2 in anhydrous solvents such as CH_2Cl_2, THF, and EtOAc. All reactions were monitored by TLC (silica-coated plates and visualizing under UV light). Light petroleum ether (bp 60–80 °C) was used. Yields refer to chromatographically and spectroscopically (^1H, ^{13}C NMR) homogeneous material. Air-sensitive reagents were transferred by syringe or double-ended needle. Evaporation of solvents was performed at reduced pressure on a Buchi rotary evaporator. ^1H and ^{13}C NMR spectra of samples in $CDCl_3$ were recorded on Varian FT-200 MHz (Gemini) and Bruker UXNMR FT-300 MHz (Avance) spectrometers. Chemical shifts (δ) are reported relative to TMS (δ = 0.0) as an internal standard. Mass spectra were recorded E1 conditions at 70 eV on LC–MSD (Agilent technologies) spectrometers. All high resolution spectra were



Scheme 3. Reagents and conditions: (a) LAH, THF, 0 °C to rt, 2 h, 70%; (b) 2,3-dihydro-2*H*-pyran, cat. PTSA, CH_2Cl_2, 0 °C, 2 h; (c) Pd/C, EtOH, 4 h, 85%; (d) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 2 h; (ii) $Ph_3P{=}CHCOOEt$, benzene, reflux, 3 h, 90% (over two steps); (e) DIBAL-H, CH_2Cl_2, 0 °C to rt, 2 h, 85%; (f) (−)-DET, $Ti(O^iPr)_4$, cumene hydroperoxide, 4 Å MS, CH_2Cl_2, −20 °C, 5 h, 75%; (g) I_2, Ph_3P, imidazole, ether/acetonitrile (3:1), 0 °C to rt, 1 h, 90%; (h) activated Zn, EtOH, reflux, 1–2 h 80%; (i) TBDMSCl, imidazole, DMAP, CH_2Cl_2, rt, 30 min, 95%; (j) comm. NH_4Cl, MeOH, reflux, 3 h, 65%.

recorded on QSTAR XL hybrid ms/ms system (Applied Biosystems/MDS sciex, foster city, USA), equipped with an ESI source (IICT, Hyderabad). Column chromatography was performed on silica gel (60–120 mesh) supplied by Acme Chemical Co., India. TLC was performed on Merck 60 F-254 silica gel plates. Optical rotations were measured with JASCO DIP-370 Polarimeter at 25 °C.

4.1.1. (3*S*)-3-{[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy}-4-pentenoic acid 6

To a stirred solution of **13** (0.84 g, 3.88 mmol) in dry CH_2Cl_2 (20 mL), $NaHCO_3$ (0.32 g, 3.88 mmol) was added at 0 °C. Dess–Martin periodinane (1.97 g, 4.65 mmol) was added and the reaction mixture was stirred at rt for 1 h. The reaction mixture was quenched with a saturated solution of $NaHCO_3$ and sodium thiosulfate (1:7) (5 mL) at 0 °C and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was washed with water (10 mL) and dried (Na_2SO_4). The solvent was evaporated and the residue was used directly for further reaction.

To a stirred solution of above aldehyde in *t*-BuOH/2-methyl 2-butene (2:1, 6 mL), $NaClO_2$ (0.5 g, 5.55 mmol), and $NaH_2PO_4{\cdot}2H_2O$ (0.86 g, 5.55 mmol) [dissolved in water (2 mL)] were added and stirred for 6 h at rt. Solvent was removed under reduced pressure and extracted with EtOAc (2 × 5 mL), the combined organic layers were washed with brine (5 mL), and dried (Na_2SO_4). The solvent was evaporated and the residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 1:9) to afford the acid **6** (0.6 g, 70% yield) as a colorless liquid. $[\alpha]_D^{25} = +1.2$ (*c* 1.2, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): 0.01 (d, 6H, *J* = 3.1 Hz), 0.82 (s, 9H), 2.40–2.51 (m, 2H), 4.50 (q, 1H, *J* = 6.2 Hz), 4.97–5.10 (d, 1H, *J* = 10.9 Hz), 5.11–5.28 (d, 1H, *J* = 17.1 Hz), 5.64–5.91 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): −5.2, −4.4, 25.7, 43.2, 70.6, 115.2, 139.6, 176.2; IR (neat): 3361, 2926, 2856, 1715 cm^{-1}; HRMS: *m/z* $[M+Na]^+$ calcd for $C_{11}H_{22}O_3SiNa$: 253.1235; found: 253.1242.

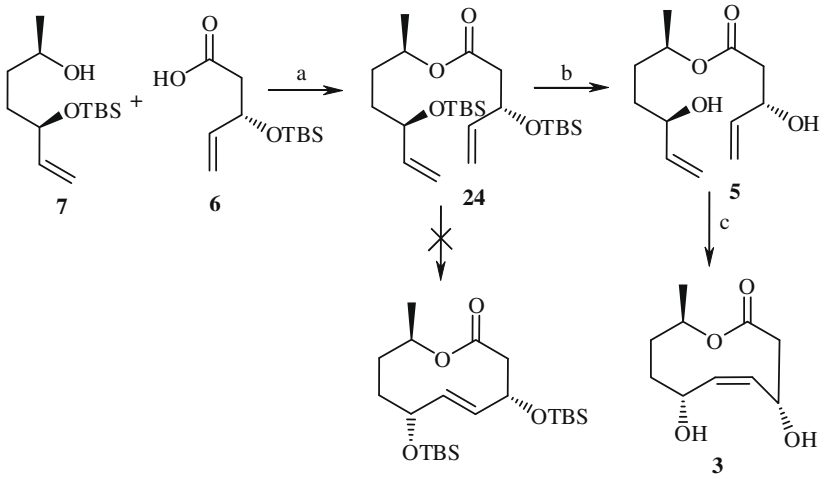
4.1.2. (2*R*)-5-(Benzyloxy)pentan-2-ol 15

To a stirred suspension of $LiAlH_4$ (1.6 g, 45.3 mmol) in dry THF (10 mL) at 0 °C was added dropwise, a solution of compound **14** (5.8 g, 30.2 mmol) in dry THF (10 mL). The reaction mixture was allowed to warm to rt, and was stirred for 4 h. It was then cooled to 0 °C, diluted with ether, and quenched with dropwise addition of saturated aqueous Na_2SO_4 (5 mL). The solid material was filtered and washed thoroughly with hot ethyl acetate for several times. The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography to afford the compound **15** (4.6 g, 80%) as a viscous liquid. $[\alpha]_D^{25} = +9.0$ (*c* 1.25, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 1.15–1.24 (d, 3H, *J* = 6.0 Hz), 1.45–1.81 (m, 4H), 2.36 (s, 1H, OH), 3.47–3.58 (t, 2H, *J* = 5.2 Hz), 3.72–3.88 (m, 1H), 4.53 (s, 2H), 7.23–7.42 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): 23.4, 26.3, 36.5, 67.7, 70.5, 73.0, 127.6, 127.7, 128.3, 138.1; IR (neat): 3423, 2926, 2857, 1454, 1365, 1097, 1027, 771, 738, 698 cm^{-1}; HRMS: *m/z* $[M+Na]^+$ calcd for $C_{12}H_{18}O_2Na$: 217.1204; found: 217.1211.

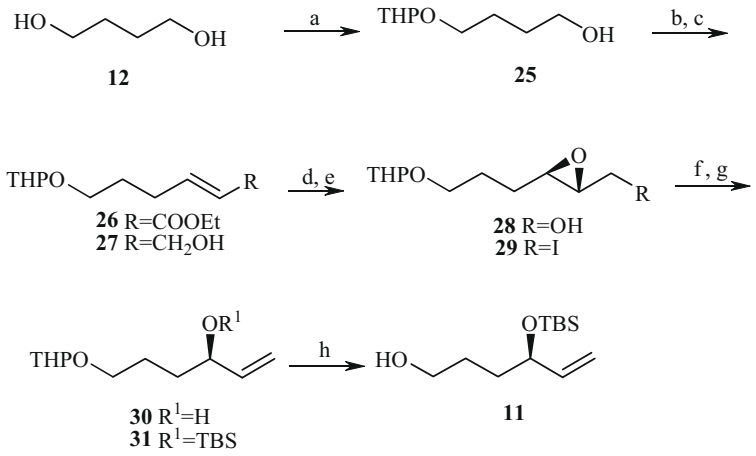
4.1.3. 2-{[(1*R*)-4-(Benzyloxy)-1-methylbutyl]oxy}tetrahydro-2*H*-pyran 16

In a 100-mL round-bottomed flask, fitted with a nitrogen adaptor, the compound **15** (4.6 g, 23.7 mmol) in dry CH_2Cl_2 (10 mL) was taken and catalytic amount of PTSA was added. Then the reaction mixture was cooled to 0 °C. To this 2*H*-3,4-dihydropyran (2.4 g, 35.5 mmol) was added dropwise. After completion of addition, the reaction mixture was allowed to stir for 3 h.

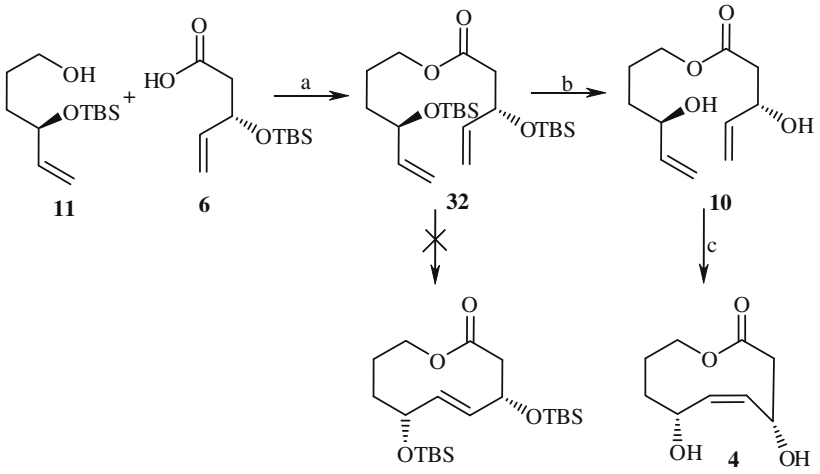
The reaction mixture was diluted with CH_2Cl_2, and the organic layer was washed with water, aq $NaHCO_3$, and dried over anhy-



Scheme 4. Reagents and conditions: (a) DCC, DMAP, CH_2Cl_2, 0 °C to rt, 6 h, 85%; (b) TBAF, THF, 0 °C, 2 h, 70%; (c) Grubbs catalyst II, CH_2Cl_2, reflux, 3 h, 70%.



Scheme 5. Reagents and conditions: (a) 2,3-dihydro-2*H*-pyran, cat. PTSA, CH_2Cl_2, 0 °C, 2 h; (b) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 2 h; (ii) Ph_3P=CHCOOEt, benzene, reflux, 3 h, 90% (over two steps); (c) DIBAL-H, CH_2Cl_2, 0 °C to rt, 2 h, 85%; (d) (−)-DET, $Ti(O^iPr)_4$, cumene hydroperoxide, 4 Å MS, CH_2Cl_2, −20 °C, 5 h, 75%; (e) I_2, Ph_3P, imidazole, ether/acetonitrile (3:1), 0 °C to rt, 1 h, 90%; (f) activated Zn, EtOH, reflux, 1–2 h 80%; (g) TBDMSCl, imidazole, DMAP, CH_2Cl_2, rt, 30 min, 95%; (h) comm. NH_4Cl, MeOH, reflux, 3 h, 65%.



Scheme 6. Reagents and conditions: (a) DCC, DMAP, CH_2Cl_2, 0 °C to rt, 6 h, 85%; (b) TBAF, THF, 0 °C, 2 h, 70%; (c) Grubbs catalyst II, CH_2Cl_2, reflux, 3 h, 70%.

drous Na_2SO_4. Concentration under reduced pressure and purification over silica gel column chromatography afforded pure tetrahydro pyranyl ether **16** (5.3 g, 81%) as a viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$): 1.06–1.24 (dd, 3H, J = 6.0, 6.8 Hz), 1.42–1.91 (m, 10H), 3.39–3.53 (m, 3H), 3.63–3.95 (m, 2H), 4.43–4.51 (d, 2H, J = 2.2 Hz), 4.52–4.72 (m, 1H), 7.16–7.41 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): 19.5, 21.4, 25.3, 26.4, 30.6, 34.1, 62.3, 67.5, 70.3, 73.2, 98.8, 127.5, 127.7, 128.4, 138.2; IR (neat): 2937, 2855, 1739, 1453, 1364, 1202, 1117, 1026, 996, 736, 698 cm^{-1}; HRMS: m/z [M+Na]$^+$ calcd for $C_{17}H_{26}O_3Na$: 301.1779; found: 301.1787.

4.1.4. (4*R*)-4-(Tetrahydro-2*H*-2-pyranyloxy)pentan-1-ol 17

To a stirred solution of **16** (5.67 g, 0.02 mmol) in EtOAc (20 mL), 10% Pd/C (catalytic) was added under hydrogen atmosphere and stirred for 4 h. Later, the reaction mixture was filtered through a pad of Celite and concentrated in vacuo. The crude residue so obtained was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 1:2.3) to afford alcohol **17** (3.06 g, 85% yield) as a brown color liquid. $[\alpha]_D^{25} = +19.6$ (c 0.65, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 1.10–1.28 (dd, 3H, J = 6.0, 6.0 Hz), 1.35–1.92 (m, 10H), 3.30–3.54 (m, 1H), 3.57–3.68 (t, 2H, J = 6.0 Hz), 3.69–3.96 (m, 2H), 4.51–4.70 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 19.6, 21.4, 25.3, 26.4, 30.6, 33.8, 62.3, 67.4, 73.9, 98.8; IR (neat): 3416, 2925, 2855, 1630, 1454, 1383, 1120, 1028, 756 cm^{-1}; HRMS: m/z [M+Na]$^+$ calcd for $C_{10}H_{20}O_3Na$: 211.1310; found: 211.1320.

4.1.5. Ethyl (*E*,6*R*)-6-(tetrahydro-2*H*-2-pyranyloxy)-2-heptenoate 18

To a stirred solution of oxalyl chloride (4.4 g, 34.68 mmol) in dry CH_2Cl_2 (40 mL) at −78 °C, dry DMSO (5.4 g, 69.2 mmol) was added dropwise. After 30 min, alcohol **17** (3.26 g, 17.3 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 (10.5 g, 103.8 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 (30 mL) and CH_2Cl_2 (3 × 40 mL). The combined organic layer was washed with water (20 mL), brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo to afford the aldehyde, which was directly used for further reaction.

To a stirred solution of above crude aldehyde in benzene (60 mL) was added (ethoxycarbonylmethylene)triphenyl phosphorane (9 g, 25.95 mmol) at rt. After 3 h, the solvent was evaporated and the residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 1:2.3) to afford **18** (3.9 g, 90% yield) as a colorless liquid. $[\alpha]_D^{25} = +5.6$ (c 1.45, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 1.08–1.20 (dd, 3H, J = 6.0, 6.0 Hz), 1.21–

1.33 (t, 3H, J = 6.8 Hz), 1.43–1.75 (m, 8H), 2.14–2.46 (m, 2H), 3.40–3.54 (m, 1H), 3.64–3.95 (m, 2H), 4.09–4.23 (q, 2H, J = 6.8 Hz), 4.51–4.69 (m, 1H), 5.72–5.86 (m, 1H), 6.84–7.05 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 14.3, 19.8, 21.6, 25.5, 30.7, 31.1, 35.6, 60.1, 62.7, 73.4, 98.9, 121.4, 149.0, 166.4; IR (neat): 3455, 2934, 2858, 1720, 1653, 1175, 1028, 989, 769 cm^{-1}; HRMS: m/z [M+Na]$^+$ calcd for $C_{14}H_{24}O_4Na$: 279.1572; found: 279.1570.

4.1.6. (*E*,6*R*)-6-(Tetrahydro-2*H*-2-pyranyloxy)-2-hepten-1-ol (19)

To a cooled (0 °C) solution of **18** (3.1 g, 12.10 mmol) in dry CH_2Cl_2 (40 mL), DIBAL-H (2.58 g, 18.16 mmol, 20% solution in toluene) was added slowly for 15 min. The reaction mixture was stirred at rt for 2 h, cooled to 0 °C, and quenched with methanol (1 mL) and sodium potassium tartarate solution (5 mL). The reaction mixture was passed through a short pad of Celite. The filtrate was concentrated and the residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 1:2.3) to afford **19** (2 g, 85% yield) as a colorless liquid. $[\alpha]_D^{25} = -1.4$ (c 1.25, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): 1.04–1.28 (dd, 3H, J = 5.8, 6.6 Hz), 1.35–1.76 (m, 8H), 1.98–2.28 (m, 2H), 3.25–3.55 (m, 1H), 3.56–4.00 (m, 2H), 4.01–4.10 (d, 2H, J = 2.9 Hz), 4.50–4.72 (m, 1H), 5.51–5.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 19.7, 21.3, 25.4, 30.6, 31.1, 36.7, 62.5, 63.6, 73.3, 98.7, 129.1, 132.9; IR (neat): 3418, 2938, 2855, 1453, 1134, 1076, 1023, 997, 972, 868 cm^{-1}; HRMS: m/z [M+Na]$^+$ calcd for $C_{12}H_{22}O_3Na$: 237.1466; found: 237.1477.

4.1.7. {(2*R*,3*R*)-3-[(3*R*)-3-(Tetrahydro-2*H*-2-pyranyloxy)butyl] oxirane-2-yl}methanol 20

In a 100-mL two-necked round-bottomed flask, 10 mL of dry CH_2Cl_2 was added to 4 Å powdered activated molecular sieves and suspension mixture was cooled to −20 °C, Ti(O^{i}Pr)$_4$ (0.58 mL, 1.96 mmol) and D (−) DET (0.4 g, 1.96 mmol) in dry CH_2Cl_2 (10 mL) were added subsequently with stirring and the resulting mixture was stirred for 30 min at −25 °C. Compound **19** (2 g, 9.8 mmol) in dry CH_2Cl_2 (20 mL) was then added and the resulting mixture was stirred for another 30 min at −25 °C followed by addition of cumenehydroperoxide (2.23 mL, 14.7 mmol) and the resulting mixture was stirred at the same temperature for 5 h. It was then warmed to 0 °C, quenched with 1 mL of water, and stirred for 1 h at rt. After that 30% aqueous NaOH solution saturated with NaCl (1 mL) was then added and the reaction mixture was stirred vigorously for another 30 min at rt. The resulting mixture was then filtered through Celite rinsing with CH_2Cl_2. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2. Combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and purified by silica gel column chromatography to afford **20** (1.69 g, 75%) as a viscous liquid. $[\alpha]_D^{25} = +15.1$ (c 1.15, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 1.06–1.28 (dd 3H, J = 5.3, 6.2 Hz), 1.39–1.92 (m, 10H), 2.81–3.02 (m, 2H), 3.29–3.52 (m, 1H), 3.53–3.66 (m, 1H), 3.66–3.95 (m, 3H), 4.51–4.68 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 19.6, 21.5, 25.4, 30.6, 31.3, 33.5, 55.8, 58.5, 62.3, 67.2, 73.5, 98.8; IR (neat): 3442, 2940, 2867, 1453, 1129, 1074, 1026, 995, 871 cm^{-1}; HRMS: m/z [M+Na]$^+$ calcd for $C_{12}H_{22}O_4Na$: 253.1415; found: 253.1423.

4.1.8. (1*R*)-3-[(2*R*,3*S*)-3-(Iodomethyl)oxiran-2-yl]-1-methylpropyl tetrahydro-2*H*-2-pyranyl ether 21

To a stirred solution of **20** (0.45 g, 1.96 mmol) in ether/acetonitrile (3:1) (20 mL), TPP (0.77 g, 2.94 mmol) and imidazole (0.26 g, 3.92 mmol) were added at 0 °C and stirred for 5 min. I_2 (0.74 g, 2.94 mmol) was added at 0 °C and stirred for 1 h. The reaction mixture was quenched with saturated sodium thiosulfate (15 mL) and extracted with EtOAc (3 × 30 mL). The organic layer was washed with water (10 mL), brine (10 mL), and dried (Na_2SO_4). The solvent was evaporated and the residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 1:9) to afford **21** (0.59 g, 90%) as a yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): 1.06–1.28 (dd 3H, J = 6.0, 6.0 Hz), 1.38–1.92 (m, 10H), 2.67–2.86 (m, 1H), 2.87–3.10 (m, 2H), 3.19–3.59 (m, 2H), 3.64–4.00 (m, 2H), 4.51–4.74 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 4.9, 19.6, 21.4, 25.4, 30.7, 31.1, 33.5, 58.2, 58.3, 67.1, 73.5, 98.9; IR (neat): 3451, 2937, 2863, 1451, 1127, 1026, 993, 872 cm^{-1}; HRMS: m/z [M+Na]$^+$ calcd for $C_{12}H_{21}O_3INa$: 363.1223; found: 363.1228.

4.1.9. (3*R*,6*R*)-6-(Tetrahydro-2*H*-2-pyranyloxy)-1-hepten-3-ol 22

To a stirred solution of **21** (0.59 g, 1.75 mmol) in EtOH (20 mL), activated Zn dust (1.14 g, 17.5 mmol) was added and stirred at reflux for 1–2 h. The reaction mixture was passed through a short pad of Celite. The filtrate was concentrated and the residue was purified by column chromatography silica gel, 60–120 mesh, EtOAc/hexane, 1:4) to afford **22** (0.29 g, 80% yield) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): 1.09–1.27 (dd 3H, J = 6.0, 6.6 Hz), 1.38–1.92 (m, 10H), 3.29–3.53 (m, 1H), 3.64–3.94 (m, 2H), 4.00–4.18 (m, 1H), 4.50–4.71 (m, 1H), 5.01–5.27 (dd, 2H, J = 10.4, 17.1 Hz), 5.75–5.93 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 19.6, 22.0, 25.4, 30.7, 31.1, 36.7, 62.3, 67.4, 73.0, 98.8, 114.5, 141.2; IR (neat): 3438, 2940, 2866, 1447, 1130, 1074, 1026, 993, 919 cm^{-1}; HRMS: m/z [M+Na]$^+$ calcd for $C_{12}H_{22}O_3Na$: 237.2108; found: 237.2112.

4.1.10. *tert*-Butyl(dimethyl)({(1*R*)-1-[(3*R*)-3-(tetrahydro-2*H*-2-pyranyloxy)butyl]-2-propenyl}oxy)silane 23

To a stirred solution of **22** (0.29 g, 1.37 mmol) in dry CH_2Cl_2 (10 mL), imidazole (0.18 g, 2.74 mmol) was added. After 5 min TBDMSCl (0.31 g, 2.05 mmol) and cat. DMAP were added and stirred at rt for 30 min. The solvent mixture was evaporated and the residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 1:24) to afford **23** (0.42 g, 95% yield) as a colorless liquid. $[\alpha]_D^{25} = -0.8$ (c 0.75, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 0.03 (d, 6H, J = 6.4 Hz), 0.89 (s, 9H), 1.05–1.23 (dd, 3H, J = 6.0, 6.2 Hz), 1.38–1.92 (m, 10H), 3.26–3.51 (m, 1H), 3.61–3.94 (m, 2H), 4.00–4.18 (m, 1H), 4.50–4.71 (m, 1H), 4.93–5.19 (dd, 2H, J = 10.2, 15.6 Hz), 5.67–5.85 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): −4.8, −4.4, 19.6, 21.9, 25.5, 25.9, 30.7, 31.1, 37.9, 62.3, 67.4, 73.7, 98.7, 113.5, 141.7; IR (neat): 3450, 2935, 2858, 1465, 1253, 1077, 1029, 996, 836, 776 cm^{-1}; ESI-MS: m/z 329 [M+H]$^+$.

4.1.11. (2*R*,5*R*)-5-{[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy}-6-hepten-2-ol 7

To the THP ether **23** (0.42 g, 1.30 mmol) in methanol (20 mL), commercial NH_4Cl (0.34 g, 6.5 mmol) was added and heated at reflux for 2–3 h. Methanol was removed, diluted with water (10 mL) and extracted with ether (3 × 20 mL). The combined ether extracts were dried over Na_2SO_4. Evaporation of solvent, followed by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 1:9) to afford THP cleaved product **7** (0.2 g, 65% yield) as a colorless liquid. $[\alpha]_D^{25} = -0.8$ (c 0.7, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): 0.04 (d, 6H, J = 3.6 Hz), 0.91 (m, 9H), 1.22–1.70 (m, 7H), 3.54–3.72 (m, 1H), 4.00–4.18 (m, 1H), 4.94–5.23 (dd, 2H, J = 10.2, 17.6 Hz), 5.65–5.90 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): −4.8, −4.4, 21.2, 25.8, 32.7, 37.7, 62.9, 73.7, 113.6, 141.6; IR (neat): 3416, 2930, 2857, 1253, 1083, 836, 773, 677 cm^{-1}; HRMS: m/z [M+Na]$^+$ calcd for $C_{13}H_{28}O_2SiNa$: 267.1756; found: 267.1769.

4.1.12. *tert*-Butyl[((1*R*,4*R*,8*S*)-8-{[1-(*tert*-butyl)-1,1-dimethylsilyl] oxy}-4-methyl-6-methylene-1-vinyl-9-decenyl)oxy]dimethylsilane 24

To a stirred solution of acid **6** (207 mg, 0.901 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C DCC and cat. DMAP were added. After 10 min alcohol **7** (222 mg, 0.902 mmol) in dry CH_2Cl_2 (10 mL) was added and stirred at rt for 6 h. The reaction mixture was

evaporated and the residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 1:24) to afford **24** (350 mg, 85% yield) as a colorless liquid. $[\alpha]_D^{25} = -7.7$ (*c* 0.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 0.02 (s, 12H), 0.87 (d, 18H, *J* = 6.8 Hz), 1.16–1.22 (d, 3H, *J* = 6.0 Hz), 1.34–1.67 (m, 4H), 2.35 (dd, 1H, *J* = 5.3, 14.3 Hz), 2.47 (dd, 1H, *J* = 7.5, 14.3 Hz), 3.98–4.12 (m, 1H), 4.49–4.59 (m, 1H), 4.78–4.92 (m, 1H), 4.96–5.25 (m, 4H), 5.66–5.89 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): −4.8, −4.4, 20.0, 25.8, 31.4, 37.6, 43.9, 64.5, 70.8, 73.6, 113.9, 114.6, 140.3, 141.3, 170.6; IR (neat): 2955, 2931, 2858, 1737, 1467, 1254, 1085, 1030, 924, 835, 776, 679 cm^{-1}; HRMS: *m/z* $[M+Na]^+$ calcd for $C_{24}H_{48}O_4Si_2Na$: 479.2988; found: 479.2984.

4.1.13. (3*S*,7*R*,10*R*)-3,10-Dihydroxy-7-methyl-1,11-dodecadiene-5-one 5

To a stirred solution of compound **24** (342 mg, 0.75 mmol) in dry THF (30 mL) at 0 °C TBAF was added and stirred at rt for 2 h. The reaction mixture was evaporated and the residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 3:7) to afford **5** (120 mg, 70% yield) as a colorless liquid. $[\alpha]_D^{25} = -6.6$ (*c* 0.75, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 1.22–1.28 (d, 3H, *J* = 6.8 Hz), 1.42–1.81 (m, 4H), 2.39–2.49 (m, 2H), 3.07 (s, 1H, OH), 4.03–4.18 (m, 1H), 4.50 (m, 1H), 4.91–5.04 (m, 1H), 5.06–5.35 (m, 4H), 5.76–5.93 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 20.0, 31.6, 36.3, 41.4, 64.6, 68.9, 72.9, 115.0, 115.3, 138.8, 140.9, 172.3; IR (neat): 3410, 2928, 2867, 1719, 1424, 1276, 1174, 925, 771 cm^{-1}; HRMS: *m/z* $[M+Na]^+$ calcd for $C_{12}H_{20}O_4Na$: 251.1259; found: 251.1270.

4.1.14. (4*S*,7*R*,10*R*)-4,7-Dihydroxy-10-methyl-3,4,7,8,9,10-hexahydro-2*H*-2-oxecinone 3

Grubbs's catalyst II (44 mg, 0.052 mmol, 10 mol %) was dissolved in CH_2Cl_2 (10 mL) and was added dropwise to a refluxing solution of the compound **5** (120 mg, 0.526 mmol) in CH_2Cl_2 (200 mL). Refluxing was continued for 3 h by which time all the starting material was consumed (TLC). The solvent was removed in vacuo, and the crude residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 7:2) to afford **3** (73 mg, 70% yield). $[\alpha]_D^{25} = -29.2$ (*c* 0.5, MeOH); ^1H NMR (400 MHz, $CDCl_3$): 1.22 (d, 3H, *J* = 6.8 Hz), 1.32–1.47 (m, 2H), 1.68–1.75 (m, 1H), 1.90–2.01 (m, 1H), 2.05–2.10 (dd, 1H, *J* = 5.9, 14.3 Hz), 2.82–2.89 (dd, 1H, *J* = 7.3, 14.3 Hz), 4.62–4.69 (m, 1H), 4.82–4.91 (m, 1H), 4.93–5.04 (m, 1H), 5.19–5.27 (m, 1H), 5.31–5.41 (dd, 1H, *J* = 9.0, 11.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 20.3, 31.4, 36.8, 43.6, 66.0, 67.4, 71.4, 133.0, 134.6, 170.5; IR (neat): 3421, 2930, 1717, 1638, 1282 cm^{-1}; HRMS: *m/z* $[M+Na]^+$ calcd for $C_{10}H_{16}O_4Na$: 223.1043; found: 223.1045.

4.1.15. 4-(Tetrahydro-2*H*-2-pyranyloxy)-1-butanol 25

The compound **25** was prepared from **12** (5 g, 55.55 mmol) as a yellow liquid in 82% yield following the procedure described for compound **16** . ^1H NMR (200 MHz, $CDCl_3$): 1.43–1.94 (m, 10H), 2.18 (s, 1H, OH), 3.32–3.56 (m, 2H), 3.64 (m, 2H), 3.71–3.91 (m, 2H), 4.58 (m, 1H); IR (neat): 3418, 2942, 2870, 1201, 1120, 1068, 1027 cm^{-1}; HRMS: *m/z* $[M+Na]^+$ calcd for $C_9H_{18}O_3Na$: 197.1516; found: 197.1513.

4.1.16. Ethyl (*E*)-6-(tetrahydro-2*H*-2-pyranyloxy)-2-hexenoate 26

The compound **26** was prepared from **25** (4.7 g, 27.52 mmol) as a yellow liquid in 90% yield following the procedure described for compound **18**. ^1H NMR (200 MHz, $CDCl_3$): 1.23–1.90 (m, 11H), 2.24–2.55 (m, 2H), 3.29–3.55 (m, 2H), 3.65–3.88 (m, 2H), 4.21 (m, 2H), 4.55 (m, 1H), 5.80 (d, 1H, *J* = 15.5 Hz), 6.86–7.15 (m, 1H); IR (neat): 2941, 2870, 1723, 1367, 1262, 1202, 1125, 1036, 982 cm^{-1}; HRMS: *m/z* $[M+Na]^+$ calcd for $C_{13}H_{22}O_4Na$: 265.2381; found: 265.2375.

4.1.17. (*E*)-6-(Tetrahydro-2*H*-2-pyranyloxy)-2-hexen-1-ol 27

The compound **27** was prepared from **26** (5.9 g, 24.38 mmol) as a yellow liquid in 80% yield following the procedure described for compound **19**. ^1H NMR (200 MHz, $CDCl_3$): 1.36–1.94 (m, 8H), 2.04–2.24 (m, 2H), 3.27–3.56 (m, 2H), 3.63–3.92 (m, 2H), 4.00–4.13 (m, 2H), 4.54 (t, 1H, *J* = 2.9 Hz), 5.61–5.73 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 19.6, 25.4, 26.0, 28.4, 30.6, 62.4, 63.5, 66.8, 98.9, 129.2, 130.2; IR (neat): 3383, 2933, 2863, 1443, 1378, 1024, 971 cm^{-1}; HRMS: *m/z* $[M+Na]^+$ calcd for $C_{11}H_{20}O_3Na$: 223.2272; found: 223.2278.

4.1.18. {(2*R*,3*R*)-3-[3-(Tetrahydro-2*H*-2-pyranyloxy)propyl]oxiran-2-yl}methanol 28

The compound **28** was prepared from **27** (3.7 g, 18.5 mmol) as a yellow liquid in 80% yield following the procedure described for compound **20**.

$[\alpha]_D^{25} = +17.5$ (*c* 2.95, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 1.42–1.94 (m, 10H), 2.90 (m, 1H), 2.98 (m, 1H), 3.34–3.55 (m, 2H), 3.57–3.69 (m, 1H), 3.70–3.92 (m, 3H), 4.57 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 19.6, 25.3, 26.0, 28.5, 30.6, 55.7, 58.4, 61.7, 62.4, 68.8, 98.9; IR (neat): 3425, 2936, 2867, 1448, 1123, 1028, 986 cm^{-1}; HRMS: *m/z* $[M+Na]^+$ calcd for $C_{11}H_{20}O_4Na$: 239.1753; found: 239.1745.

4.1.19. 2-{3-[(2*R*,3*S*)-3-(Iodomethyl)oxiran-2-yl]propoxy}tetrahydro-2*H*-2-pyran 29

The compound **29** was prepared from **28** (3.5 g, 16.20 mmol) as a yellow liquid in 93% yield following the procedure described for compound **21**. $[\alpha]_D^{25} = -3.8$ (*c* 2.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 1.41–1.91 (m, 10H), 2.81 (m, 1H), 2.91–3.04 (m, 2H), 3.20–3.33 (m, 1H), 3.35–3.54 (m, 2H), 3.68–3.88 (m, 2H), 4.56 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 4.8, 19.5, 25.3, 26.0, 28.6, 30.6, 56.5, 58.2, 62.2, 66.7, 98.8; IR (neat): 3449, 2940, 2867, 1447, 1125, 1031, 900 cm^{-1}; HRMS: *m/z* $[M+Na]^+$ calcd for $C_{11}H_{19}O_3INa$: 349.2354; found: 349.2341.

4.1.20. (3*R*)-6-(Tetrahydro-2*H*-2-pyranyloxy)-1-hexen-3-ol 30

The compound **30** was prepared from **29** (4 g, 12.2 mmol) as a yellow liquid in 80% yield following the procedure described for compound **22**. $[\alpha]_D^{25} = -9.1$ (*c* 0.45, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 1.34–1.92 (m, 10H), 2.26 (s, 1H, OH), 3.31–3.53 (m, 2H), 3.68–3.88 (m, 2H), 4.12 (m, 1H), 4.58 (m, 1H), 5.07 (d, 1H, *J* = 10.5 Hz), 5.22 (d, 1H, *J* = 17.3 Hz), 5.74–5.92 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 19.5, 25.3, 26.0, 30.6, 34.2, 62.0, 67.4, 73.4, 98.8, 113.8, 141.5; IR (neat): 3447, 2925, 2855, 1638, 1121, 1028, 990, 759 cm^{-1}; HRMS: *m/z* $[M+Na]^+$ calcd for $C_{11}H_{20}O_3Na$: 223.1936; found: 223.1932.

4.1.21. *tert*-Butyl(dimethyl)({(1*R*)-1-[3-(tetrahydro-2*H*-2-pyranyloxy)propyl]-2-propenyl}oxy)silane 31

The compound **31** was prepared from **30** (1 g, 3.34 mmol) as a yellow liquid in 95% yield following the procedure described for compound **23**. $[\alpha]_D^{25} = -7.1$ (*c* 1.95, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 0.02 (s, 3H), 0.04 (s, 3H), 0.89 (s, 9H), 1.34–1.92 (m, 10H), 3.27–3.54 (m, 2H), 3.60–3.90 (m, 2H), 4.07–4.19 (m, 1H), 4.55 (s, 1H), 5.01 (d, 1H, *J* = 9.8 Hz), 5.13 (d, 1H, *J* = 17.3 Hz), 5.68–5.88 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): −4.8, −4.4, 19.5, 25.3, 25.4, 25.8, 30.7, 34.6, 62.2, 67.5, 73.5, 98.6, 113.6, 141.5; IR (neat): 2933, 2858, 1467, 1253, 1032, 836, 775 cm^{-1}; HRMS: *m/z* $[M+Na]^+$ calcd for $C_{17}H_{34}O_3SiNa$: 337.2879; found: 337.2883.

4.1.22. (4*R*)-4-{[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy}-5-hexen-1-ol 11

The compound **11** was prepared from **31** (1 g, 3.34 mmol) as a yellow liquid in 65% yield following the procedure described for compound **7**. $[\alpha]_D^{25} = -5.3$ (*c* 2.55, $CHCl_3$); ^1H NMR (300 MHz,

$CDCl_3$): 0.01 (s, 3H), 0.02 (s, 3H), 0.87 (s, 9H), 1.46–1.64 (m, 4H), 1.78 (br s, 1H, OH), 3.50–3.64 (m, 2H), 4.09–4.19 (m, 1H), 4.97–5.04 (d, 1H, J = 10.5 Hz), 5.06–5.16 (d, 1H, J = 16.6 Hz), 5.67–5.82 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): −4.9, −4.5, 25.8, 28.0, 34.4, 62.8, 73.4, 113.9, 141.0; IR (neat): 3365, 2930, 2857, 1467, 1253, 1058, 1029, 835, 776 cm^{-1}; HRMS: m/z $[M+Na]^+$ calcd for $C_{12}H_{26}O_2SiNa$: 231.1307; found: 231.1298.

4.1.23. *tert*-Butyl[((1*R*,8*S*)-8-{[1-(*tert*-butyl)-1,1-dimethylsilyl] oxy}-6-methylene-1-vinyl-9-decenyl)oxy]dimethylsilane 32

The compound **32** was prepared from **6** (200 mg, 0.87 mmol) as a yellow liquid in 80% yield following the procedure described for compound **24**. $[\alpha]_D^{25} = -2.8$ (c 0.7, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): 0.04 (s, 12H), 0.88 (d, 18H, J = 5.4 Hz), 1.44–1.76 (m, 4H), 2.31–2.44 (dd, 1H, J = 5.4, 14.8 Hz), 2.44–2.58 (dd, 1H, J = 7.8, 14.8 Hz), 3.97–4.18 (m, 3H), 4.48–4.62 (m, 1H), 4.97–5.28 (m, 4H), 5.63–5.94 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): −4.8, −4.4, 25.7, 25.8, 34.2, 43.7, 64.6, 70.8, 73.2, 114.0, 114.6, 140.2, 141.25, 171.1; IR (neat): 3425, 2924, 2853, 1742, 1462, 1381, 1265, 1118 cm^{-1}; HRMS: m/z $[M+Na]^+$ calcd for $C_{23}H_{46}O_4Si_2Na$: 465.2133; found: 465.2139.

4.1.24. (4*R*)-4-Hydroxy-5-hexenyl(3*S*)-3-hydroxy-4-pentenoate 10

The compound **10** was prepared from **32** (300 mg, 0.67 mmol) as a yellow liquid in 70% yield following the procedure described for compound **5**. $[\alpha]_D^{25} = -3.8$ (c 0.55, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 1.53–1.82 (m, 4H), 2.43–2.60 (m, 2H), 3.33 (s, 1H, OH), 4.05–4.22 (m, 3H), 4.51 (m, 1H), 4.06–5.37 (m, 4H), 5.77–5.94 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 24.5, 33.0, 41.2, 64.6, 68.9, 72.5, 115.0, 115.4, 138.7, 140.7, 172.2; IR (neat): 3427, 2926, 1723, 1643, 1423, 1278, 1175, 992, 926, 767 cm^{-1}; HRMS: m/z $[M+Na]^+$ calcd for $C_{11}H_{18}O_4Na$: 237.1102; found: 237.1105.

4.1.25. (4*S*,7*R*)-4,7-Dihydroxy-3,4,7,8,9,10-hexahydro-2*H*-2-oxecinone 4

The compound **4** was prepared from **10** (100 mg, 0.46 mmol) in 70% yield following the procedure described for compound **3**. ^{1}H NMR (300 MHz, $CDCl_3$): 1.25–1.38 (m, 2H), 1.47–1.57 (m, 1H), 1.89–1.98 (m, 1H), 1.98–2.10 (dd, 1H, J = 5.6, 14.8 Hz), 2.25 (s, 1H, OH), 2.75–2.89 (dd, 1H, J = 7.5, 14.8 Hz), 4.20–4.29 (t, 2H, J = 7.0 Hz), 4.35–4.44 (m, 1H), 4.68–4.78 (m, 1H), 5.15–5.25 (m, 1H), 5.46–5.59 (dd, 1H, J = 9.7, 11.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 25.0, 33.4, 41.6, 65.4, 69.0, 71.6, 131.4, 133.6, 170.8; IR (neat): 3425, 2929, 1724, 1264 cm^{-1}; HRMS: m/z $[M]^+$ calcd for $C_9H_{14}O_4$: 186.1041; found: 186.1048.

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