Tetrahedron: *Asymmetry* 20 (2009) 2205–2210

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Total synthesis of the marine polypropionates, siphonarienal, siphonarienone, and pectinatone

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ARTICLE INFO

Article history:
Received 20 July 2009
Accepted 20 August 2009
Available online 26 September 2009

ABSTRACT

The synthesis of the marine natural products, siphonarienal, siphonarienone, and pectinatone is described employing desymmetrization strategy to create three consecutive stereogenic centers. The key intermediate **7** was made by asymmetric hydroboration of the known *meso*-olefin using (−)-IPC_2BH followed by PCC and Baeyer-Villiger oxidation reactions.

1. Introduction

Marine mollusks of the genus *Siphonaria* are a rich source of polypropionates,[1] polyether antibiotics,[2] and macrolides.[3] Natural products derived from marine mollusks have gained interest due to their bio-active secondary metabolites[1,4] and their unusual structures. Siphanarienes **1** and **2** and pectinatone **3** are marine polypropionate natural products produced from the genus *Siphonaria* such as *Siphonariea grisea*[5] and *Siphonaria pectinata*,[6] respectively, collected from the intertidal region of the Mediterranean sea and Atlantic ocean. The members of this class all contain an alternating 1,3-*syn* arrangement of methyl substituents in their respective aliphatic chains connected through an olefinic linker to a more polar oxygen-containing group.[7] This structural motif offers a significant challenge for asymmetric synthesis. They are active against Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*), yeast (*Candida albicans* and *Saccharomyces cervisiae*), and several human cancer cell lines.[5b,8] The structures of **1**–**3** were established on the basis of their spectroscopic data and X-ray diffraction analysis.[5a,9]

Most of the reports which have appeared for the synthesis of these compounds mainly used iterative alkylations or diastereoselective aldol reactions.[10–12] Other methods include the iterative application of CuI-Tol-BINAP-catalyzed asymmetric conjugative addition[13] and Zr-catalyzed asymmetric carboalumination.[14] Herein, we report the synthesis of polypropionates **1**–**3** (Fig. 1) utilizing desymmetrization strategy to set the stereochemistry of the trimethylnonyl unit.

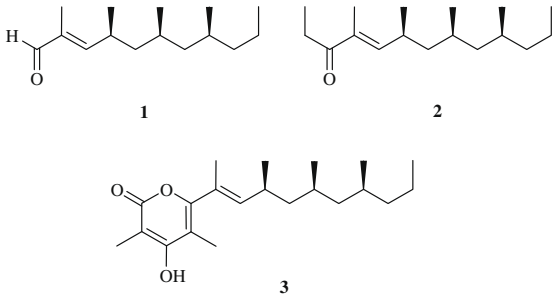

Figure 1.

2. Results and discussion

The retrosynthesis is depicted in Scheme 1. Compound **1** and **3** could be obtained from **4**, which could be derived from **5**. Compound **2** could be prepared directly from **5**, which in turn could be prepared from **6**. Compound **6** is accessible from the known precursor **7**.

Our synthesis began with the known precursor **7**.[15] Accordingly, allylation of **7** with allyl bromide in the presence of LHMDS in anhydrous THF at −78 °C gave compound **8** in 94% yield. Reductive ring opening of **8** with LAH in anhydrous THF gave triol **6** in 90% yield. The 1,3-diol of **6** was protected as acetonide **9** using 2,2-dimethoxypropane and a catalytic amount of CSA, in CH_2Cl_2/Et_2O followed by protection of the primary hydroxyl group as its benzyl ether **10**. Next, the acetonide group was hydrolyzed to yield diol **11** and the primary hydroxyl group was selectively tosylated with TsCl, Et_3N, and DMAP in CH_2Cl_2 to furnish monotosylate **12** followed by reductive cleavage[16] ($LiAlH_4$, THF, 80%) of the sulfonate leading to the formation of **13**. The secondary hydroxyl group was converted into the xanthate ester and reduced to give compound **15**. Oxidative removal of the PMB group using DDQ yielded alcohol **16**, which was converted to the xanthate and reduced to provide compound **18**. Debenzylation and reduction of the terminal olefin were successfully achieved in one-pot using Pd/C and H_2, in HPLC grade EtOAc to give alcohol **19**, which on oxidation using IBX provided the corresponding aldehyde **5** (Scheme 2).

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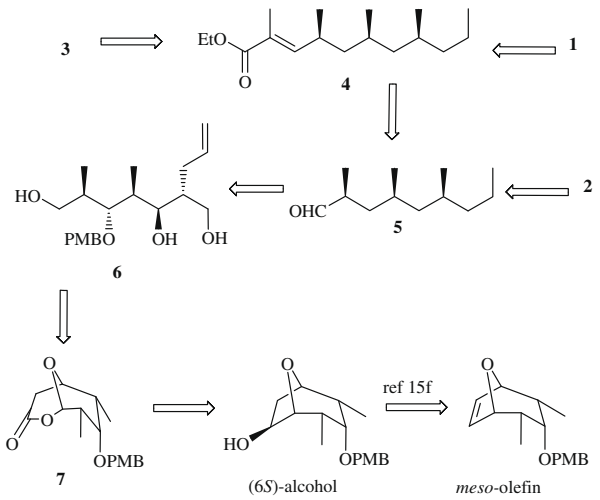
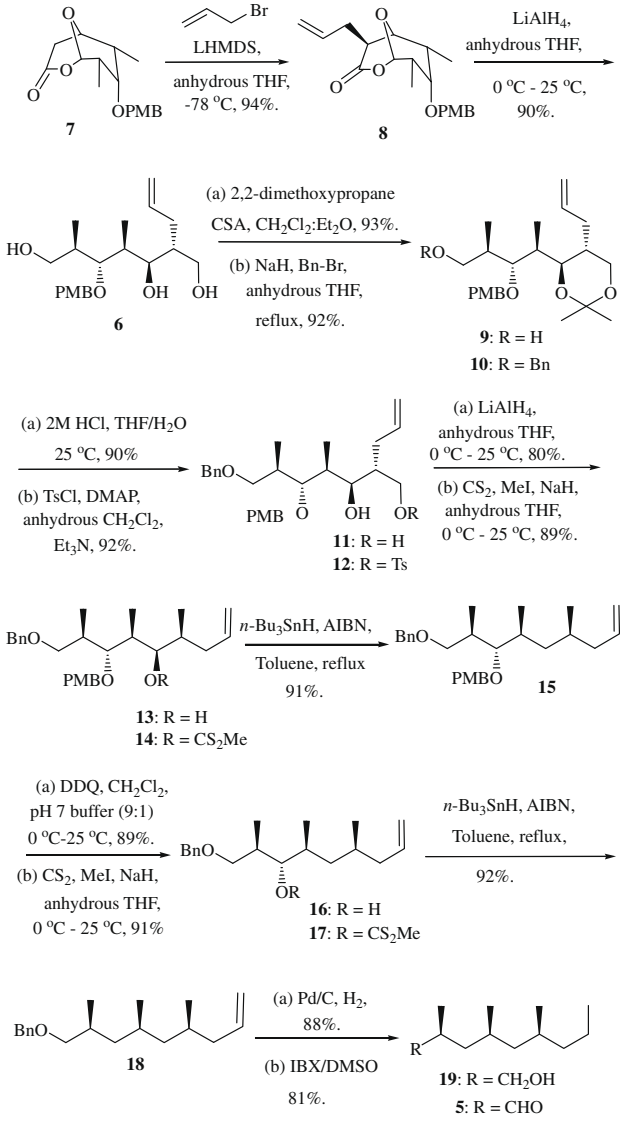
doi:10.1016/j.tetasy.2009.08.021



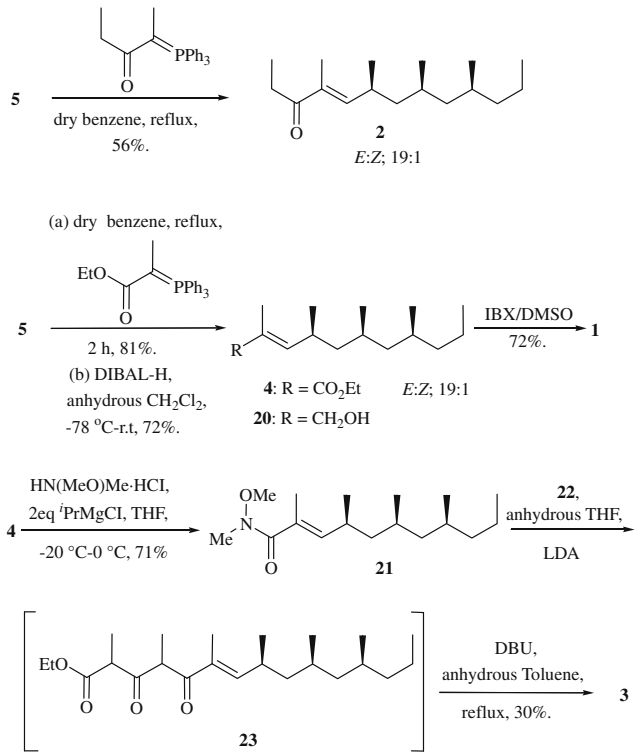
Scheme 1. Retrosynthetic analysis.



Scheme 2.

Aldehyde **5** was utilized for the synthesis of target molecules **1**–**3**. Aldehyde **5** was subjected to a Wittig reaction using 2-(1,1,1-triphenyl-λ^5-phosphanylidene)-3-pentanone in refluxing anhydrous benzene to give siphonarienone **2** in 56% yield.

To prepare target compounds **1** and **3**, aldehyde **5** was subjected to a Wittig reaction using ethyl 2-(1,1,1-triphenyl-λ^5-phosphanylidene)propanoate in refluxing anhydrous benzene to give ester **4**. The ester was reduced to allylic alcohol **20** and further oxidized to afford siphonarienal **1**. Whereas treatment of ester **4** with *N*-methoxy, *N*-methyl ammonium chloride, and ^{i}PrMgCl, in anhydrous THF, at −20 to 0 °C afforded Weinreb amide **21** in 71% yield, which on treatment with ethyl 2-methyl-3-oxopentanoate **22**[17] followed by cyclization of the resulting β,δ-diketo ester **23** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing toluene[18] gave the target molecule, pectinatone **3** (Scheme 3).



Scheme 3.

Most of the previous syntheses involved three steps for the generation of each additional stereogenic center with a stoichiometric amount or even excesses of chiral carboxamides and related reagents. Thus, the synthesis of target molecules **1**–**3** containing three stereogenic centers typically requires approximately 10 steps from readily available compounds. However, the present synthesis utilizing desymmetrization strategy creates three consecutive stereogenic centers in a single reaction to give an intermediate **6,** which is an attractive advantage over the reported methods.

3. Conclusions

We have achieved the total synthesis of siphonarienal, siphonarienone, and pectinatone using desymmetrization strategy to set the asymmetric carbon centers.

4. Experimental section

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 (^{1}H, ^{13}C NMR) homogeneous material. Air-sensitive reagents were transferred by a syringe or double-ended needle. Evaporation of solvents was performed at reduced pressure on a Büchi rotary evaporator. ^{1}H 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) were reported relative to TMS (δ = 0.0) as an internal standard. Mass spectra were recorded in E1 conditions at 70 eV on LC-MSD (Agilent technologies) spectrometers. All high-resolution spectra were 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. 7-(4-Methoxybenzyloxy)-4(2′-propen),6,8-diimethyl-(1*S*,4*S*,5*S*,6*S*,7*S*,8*R*)-2,9-dioxabicyclo-[3.3.1]nonan-3-one 8

To a stirred solution of lactone **7** (16.5 g, 53.92 mmol) in anhydrous THF (150 mL) at −78 °C under a nitrogen atmosphere, was added LHMDS (70.09 mL, 70.09 mmol, 1.0 M) dropwise. After one-hour stirring at −78 °C, allylbromide (neat 27.39 mL, 323.52 mmol) was added dropwise. The reaction mixture was stirred for 1 h at the same temperature and quenched with saturated aqueous NH_4Cl solution (30 mL) and extracted with ether (3 × 100 mL). The organic extracts were washed with water and brine, and dried over anhydrous Na_2SO_4 (2 g), concentrated in vacuo, and purified by column chromatography (1:4, EtOAc/hexane) to afford allyl lactone **8** (17.53 g, 94%) as a white crystalline solid. Mp = 97–98 °C; R_f = 0.55 (EtOAc/hexane, 3:7); $[\alpha]_D^{25} = -75$ (*c* 1.3, $CHCl_3$); IR (neat): ν_{max} 2968, 1730, 1608, 1512, 1459, 1258, 1215 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.3 Hz, 2H, ArH), 6.82 (d, *J* = 8.3 Hz, 2H, ArH), 5.70 (m, 1H), 5.35 (d, *J* = 2.2 Hz, 1H, CH), 5.16–5.04 (m, 2H), 4.60 (d, *J* = 11.3 Hz, 1H, CH), 4.38 (d, *J* = 11.3 Hz, 1H, CH), 3.82 (d, *J* = 4.5 Hz, 1H, CH), 3.78 (s, 3H, CH_3), 3.53 (t, *J* = 3.0 Hz, 1H, CH), 2.66–2.54 (m, 2H), 2.44 (dd, *J* = 3.0, 9.0 Hz, 1H, CH), 2.18 (m, 1H, CH), 2.0 (m, 1H, CH), 1.14 (d, *J* = 6.8 Hz, 3H, CH_3), 0.87 (d, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 159.0, 135.3, 132.0, 129.0, 118.0, 113.5, 99.9, 78.6, 76.0, 72.6, 55.1, 40.3, 39.6, 37.6, 37.4, 13.4, 13.2; HRMS (ESI): $[M+Na]^+$ *m/z* calcd for $C_{20}H_{26}O_5Na$: 369.1677, found: 369.1671 (−1.8797 ppm error).

4.1.2. (2*R*,3*R*,4*S*,5*R*,6*R*)-2-Allyl-5-[(4-methoxybenzyl)oxy]-4,6-dimethylheptane-1,3,7-triol 6

To a stirred suspension of $LiAlH_4$ (3.77 g, 99.42 mmol) in anhydrous THF (150 mL) at 0 °C was added dropwise a solution of allyl lactone **8** (17.2 g, 49.71 mmol) in anhydrous THF (30 mL). The reaction mixture was allowed to warm to 25 °C and stirred for 2 h. The reaction mixture was then cooled to 0 °C and quenched by dropwise addition of saturated aqueous Na_2SO_4 (30 mL). The precipitate formed was filtered and washed with ethyl acetate. The combined organic extracts were dried over Na_2SO_4 (1 g) and concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography (3:7, EtOAc/hexane) to afford the pure product **6** (15.74 g, 90%) as a viscous liquid. R_f = 0.23 (EtOAc/hexane, 3:7); $[\alpha]_D^{25} = +6.0$ (*c* 1.4, $CHCl_3$); IR (neat): ν_{max} 3412, 2967, 2929, 1613, 1514, 1461, 1301, 1249, 1176, 1034 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.0 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 5.84–5.60 (m, 1H), 5.08–4.94 (m, 2H), 4.59 (ABq, *J* = 15.3 Hz, 2H, ArH–CH_2), 3.98–3.56 (m, 4H, CH), 3.80 (s, 3H, CH_3), 3.70 (dd, *J* = 2.9, 10.9 Hz, 1H, CH), 3.49 (dd, *J* = 2.9, 9.5 Hz, 1H, CH), 2.11–1.48 (m, 5H, allylic-CH_2, 3 × CH), 1.14 (d, *J* = 7.3 Hz, 3H, CH_3), 0.95 (d, *J* = 6.6 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 135.6, 129.7, 129.4, 116.5, 113.8, 87.7, 75.7, 74.2, 65.1, 64.6, 55.0, 41.7, 37.6, 35.2, 32.5, 14.6, 11.5; HRMS (ESI): $[M+Na]^+$ *m/z* calcd for $C_{20}H_{32}O_5Na$: 375.2147, found: 375.2159 (+3.0804 ppm error).

4.1.3. (2*R*,3*R*,4*R*)-4-[(4*R*,5*R*)-5-Allyl-2,2-dimethyl-1,3-dioxan-4-yl]-3-[(4-methoxybenzyl)oxy]-2-methylpentan-1-ol 9

2,2-Dimethoxypropane (25.9 mL, 213.0 mmol) and CSA (1.95 g, 42.61 mmol) were added successively to a solution of triol **6** (15 g, 42.61 mmol) in a mixture of CH_2Cl_2:Et_2O (9:1) (150 mL). The solution was stirred for 1 h at room temperature and then quenched with saturated aqueous $NaHCO_3$ (30 mL). The aqueous layer was extracted with ether (3 × 100 mL). The organic layers were washed with brine, dried over Na_2SO_4 (1 g), and concentrated. The crude compound was purified on column chromatography (1:3, EtOAc/hexane) to afford the monoacetonide **9** (15.53 g, 93%) as a viscous liquid. R_f = 0.37 (EtOAc/hexane, 1:3); $[\alpha]_D^{25} = -39.5$ (*c* 3.41, $CHCl_3$); IR (neat): ν_{max} 3456, 2972, 2930, 1613, 1513, 1460, 1379, 1299, 1247, 1198, 1038 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 5.76–5.60 (m, 1H), 5.06–4.96 (m, 2H), 4.54 (ABq, *J* = 10.7 Hz, 2H, ArH–CH_2), 3.98 (dd, *J* = 1.3, 10.0 Hz, 1H, C*H*$_a$H$_b$), 3.84 (dd, *J* = 3.0, 10.7 Hz, 1H, CH), 3.79 (s, 3H, OCH_3), 3.74 (dd, *J* = 4.9, 11.5 Hz, 1H, CH), 3.53 (m, 2H, CH_2), 3.43 (dd, *J* = 2.2, 9.8 Hz, 1H, CH$_a$*H*$_b$), 2.67 (br s, 1H, OH), 2.13–1.72 (m, 5H, 3 × CH, allylic-CH_2), 1.38 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.20 (d, *J* = 7.2 Hz, 3H, CH_3), 0.87 (d, *J* = 7.0 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 134.8, 130.4, 128.4, 116.6, 113.6, 97.6, 84.8, 74.8, 71.3, 63.84, 63.78, 54.9, 37.1, 36.0, 34.4, 32.3, 29.3, 19.6, 16.1, 9.7; HRMS (ESI): $[M+Na]^+$ *m/z* calcd for $C_{23}H_{36}O_5Na$: 415.2460, found: 415.2470 (+2.3014 ppm error).

4.1.4. (4*R*,5*R*)-5-Allyl-4-(1*R*,2*R*,3*R*)-4-(benzyloxy)-2-[(4-methoxybenzyl)oxy]-1,3-dimethylbutyl-2,2-dimethyl-1,3-dioxane 10

To a stirred suspension of NaH (3.66 g, 76.53 mmol) in anhydrous THF (150 mL) under a nitrogen atmosphere was added monoacetonide **9** (15.0 g, 38.26 mmol) in anhydrous THF (50 mL) dropwise at 0 °C. The reaction mixture was allowed to warm to 25 °C and then heated at reflux for 1 h. It was then cooled to 25 °C, and benzyl bromide (5.0 mL, 42.09 mmol) was added dropwise, refluxed for 3 h, and cooled to 0 °C. It was then quenched with ice and extracted with ether (3 × 100 mL). The combined extracts were washed with brine, dried over Na_2SO_4 (1 g), and purified by column chromatography (1:9, EtOAc/hexane) to afford **10** (16.96 g, 92%) as a colorless oil. R_f = 0.41 (EtOAc/hexane, 1:9); $[\alpha]_D^{25} = -18.0$ (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33–7.20 (m, 5H, ArHH), 7.16 (d, *J* = 8.3 Hz, 2H, ArHH), 6.81 (d, *J* = 8.3 Hz, 2H, ArHH), 5.65 (m, 1H), 5.06–4.91 (m, 2H), 4.51 (ABq, *J* = 10.5, 17.3 Hz, 2H, ArH–CH_2), 4.45 (s, 2H, ArH–CH_2), 3.94 (m, 1H), 3.79 (s, 3H, CH_3), 3.71 (dd, *J* = 4.5, 11.3 Hz, 1H, CH), 3.62 (dd, *J* = 5.3, 9.0 Hz, 1H, CH), 3.48 (t, *J* = 10.5 Hz, 1H, CH), 3.38–3.27 (m, 2H), 2.14 (m, 1H, CH), 2.07–1.91 (m, 2H), 1.89–1.64 (m, 2H), 1.34 (s, 3H, CH_3), 1.33 (s 3H, CH_3), 1.10 (d, *J* = 6.8 Hz, 3H, CH_3), 0.87 (d, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.8, 138.7, 135.1, 129.3, 128.3, 128.2, 127.3, 127.2, 116.6, 113.6, 97.8, 82.8, 74.4, 73.0, 71.8, 71.6, 64.1, 55.1, 36.9, 35.9, 34.7, 32.4, 29.5, 19.7, 16.7, 9.9; HRMS (ESI): $[M+Na]^+$ *m/z* calcd for $C_{30}H_{42}O_5Na$: 505.2929, found: 505.2906 (−4.7390 ppm error).

4.1.5. (2*R*,3*R*,4*S*,5*R*,6*R*)-2-Allyl-7-(benzyloxy)-5-[(4-methoxybenzyl)oxy]-4,6-dimethylheptane-1,3-diol 11

To a stirred solution of **10** (16 g, 33.19 mmol) in THF (120 mL) was added aqueous 2 M HCl (83.0 mL, 165.97 mmol), and the resulting reaction mixture was stirred for 5 h at 25 °C. It was diluted with EtOAc and the aqueous layer was extracted twice with EtOAc (2 × 100 mL). The combined organic layers were washed

with brine, dried over anhydrous Na_2SO_4 (1 g), and the solvent was evaporated under reduced pressure and purified by column chromatography (1:3, EtOAc/hexane) to afford the diol **11** (13.2 g, 90%) as a viscous liquid. R_f = 0.48 (EtOAc/hexane, 2:3); $[\alpha]_D^{25} = +18.0$ (*c* 1.15, $CHCl_3$); IR (neat): ν_{max} 3441, 2966, 2926, 1612, 1513, 1301, 1249, 1175, 1035 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.30 (m, 5H, ArH), 7.10 (d, *J* = 8.8 Hz, 2H, ArH), 6.80 (d, *J* = 8.1 Hz, 2H, ArH), 5.70 (m, 1H), 5.07–4.91 (m, 2H), 4.48 (s, 2H, ArH–CH_2), 4.47 (ABq, *J* = 10.2 Hz, 2H, ArH–CH_2), 3.91 (m, 2H, CH_2), 3.79 (s, 3H, O–CH_3), 3.67 (dd, 4.4, 8.8 Hz, 1H, CH), 3.62 (m, 1H), 3.52 (dd, *J* = 1.4, 9.5 Hz, 1H, CH), 3.44 (dd, *J* = 2.9, 8.8 Hz, 1H, CH), 3.27 (br s, 1H, OH), 2.17–1.66 (m, 5H), 1.11 (d, *J* = 7.3 Hz, 3H, CH_3), 0.99 (d, *J* = 6.6 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.4, 138.3, 135.9, 129.9, 129.3, 128.3, 127.6, 127.5, 116.6, 113.9, 86.8, 75.7, 74.6, 73.2, 72.0, 65.5, 54.9, 41.9, 36.7, 34.7, 32.9, 15.1, 12.1; HRMS (ESI): $[M+Na]^+$ *m/z* calcd for $C_{27}H_{38}O_5Na$: 465.2616, found: 465.2595 (−4.7165 ppm error).

4.1.6. (2*R*)-2-(1*R*,2*S*,3*R*,4*R*)-5-(Benzyloxy)-1-hydroxy-3-[(4-methoxybenzyl)oxy]-2,4-dimethylpentyl-4-pentenyl 4-methyl-1-benzenesulfonate 12

To a stirred solution of alcohol **11** (13 g, 29.41 mmol) in anhydrous Et_3N (12.25 mL, 88.23 mmol) at 0 °C was added *p*-toluenesulfonylchloride (6.16 g, 32.35 mmol). After the reaction mixture was stirred at 25 °C for 1.5 h, the reaction was quenched with water (50 mL) and the resultant mixture was then extracted with EtOAc (2 × 100 mL). The extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4 (1 g), and concentrated in vacuo. Purification of the residue by column chromatography (1:9, EtOAc/hexane) afforded **12** (16.12 g, 92%) as a liquid. R_f = 0.4 (EtOAc/hexane, 1:4); ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.5 Hz, 2H, ArH), 7.29 (m, 5H, ArH), 7.25 (d, *J* = 7.5 Hz, 2H, ArH), 7.08 (d, *J* = 9.0 Hz, 2H, ArH), 6.79 (d, *J* = 8.3 Hz, 2H, ArH), 5.63 (m, 1H), 5.07–4.93 (m, 2H), 4.48 (s, 2H, Ph–CH_2), 4.46 (ABq, *J* = 12.0 Hz, 2H, Ar–CH_2), 4.12 (m, 2H, O–CH_2), 3.79 (s, 3H, O–CH_3), 3.72 (dd, *J* = 0.7, 9.0 Hz, 1H, Ph–CH_2–O–CH_aH_b), 3.63 (dd, *J* = 4.5, 9.0 Hz, 1H, CH), 3.48 (dd, *J* = 1.5, 9.0 Hz, 1H, Ph–CH_2–O–CH_aH_b), 3.43 (dd, *J* = 3.0, 8.3 Hz, 1H, CH), 3.37 (br s, 1H, OH), 2.40 (s, 3H, CH_3), 2.10–1.66 (m, 5H), 0.99 (d, *J* = 6.7 Hz, 3H, CH_3), 0.97 (d, *J* = 6.7 Hz, 3H, CH_3).

4.1.7. (4*S*,5*R*,6*S*,7*R*,8*R*)-9-(Benzyloxy)-7-[(4-methoxybenzyl)-oxy]-4,6,8-trimethyl-1-nonen-5-ol 13

To a stirred suspension of $LiAlH_4$ (2.04 g, 53.69 mmol) in anhydrous THF (10 mL) at 0 °C was added dropwise a solution of tosylated compound **12** (16.0 g, 26.84 mmol) in anhydrous THF (100 mL). The reaction mixture was refluxed for 1 h. It was then cooled to 0 °C, diluted with ether, and quenched with the dropwise addition of saturated aqueous Na_2SO_4 (50 mL). The solid material was filtered and washed thoroughly with hot EtOAc (4 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 (1 g). The solvent was removed under vacuo and the residue was purified by column chromatography (1:14, EtOAc/hexane) to afford the compound **13** (9.14 g, 80%) as a colorless liquid. R_f = 0.5 (EtOAc/hexane, 2:23); $[\alpha]_D^{25} = +26.6$ (*c* 1.15, $CHCl_3$); IR (neat): ν_{max} 3479, 2967, 2912, 1613, 1586, 1514, 1454, 1302, 1249, 1068, 1036 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (m, 5H, ArH), 7.11 (d, *J* = 9.0 Hz, 2H, ArH), 6.79 (d, *J* = 8.3 Hz, 2H, ArH), 5.73 (m, 1H), 5.04–4.89 (m, 2H), 4.47 (s, 2H, ArH–CH_2), 4.46 (ABq, *J* = 10.5 Hz, 2H, ArH–CH_2), 3.78 (s, 3H, CH_3), 3.65 (dd, *J* = 4.5, 8.3 Hz, 1H, CH), 3.55–3.49 (m, 2H, CH_2), 3.45 (dd, *J* = 3.0, 8.3 Hz, 1H, CH), 2.07 (m, 2H, CH_2), 1.94 (m, 1H, CH), 1.78–1.55 (m, 2H, 2 × CH), 1.06 (d, *J* = 6.8 Hz, 3H, CH_3), 0.99 (d, *J* = 6.8 Hz, 3H, CH_3), 0.96 (d, *J* = 6.0 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 138.4, 136.6, 129.3, 129.0, 128.3, 127.6, 127.4, 116.0, 113.7, 87.0, 75.5, 74.2, 73.0, 72.2, 55.1, 37.1, 36.6, 35.7, 34.4, 16.1, 15.0, 11.7; HRMS (ESI): $[M+Na]^+$ *m/z* calcd for $C_{27}H_{38}O_4Na$: 449.2667, found: 449.2654 (−3.0711 ppm error).

4.1.8. (1*R*,2*S*)-1-(1*R*,2*R*,3*R*)-4-(Benzyloxy)-2-[(4-methoxybenzyl) oxy]-1,3-dimethylbutyl-2-methyl-4-pentenyl (methylsulfanyl)methanethioate 14

To a solution of sodium hydride (1.0 g, 41.66 mmol) in anhydrous THF (30 mL) the alcohol **13** (8.8 g, 20.65 mmol) in anhydrous THF (20 mL) was added at 0 °C and allowed to stir at room temperature for 0.5 h. To this reaction mixture, carbon disulfide (3.73 mL, 61.97 mmol) and iodomethane (2.56 mL, 41.31 mmol) were added at 0 °C. The mixture was stirred at room temperature for 2 h. After completion of the reaction at 0 °C, it was quenched by the slow addition of crushed ice. The mixture was raised to room temperature and separated, and the aqueous layer was washed with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were dried (Na_2SO_4), concentrated in vacuo, and purified by column chromatography (1:14, EtOAc/hexane) to afford **14** (9.48 g, 89%). R_f = 0.62 (EtOAc/hexane, 1:13); $[\alpha]_D^{25} = +2.3$ (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 2969, 2924, 1612, 1513, 1457, 1300, 1241, 1172, 1048 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (m, 5H, ArH), 7.18 (d, *J* = 8.5 Hz, 2H, ArH), 6.79 (d, *J* = 8.6 Hz, 2H, ArH), 6.02 (dd, *J* = 3.9, 5.6 Hz, 1H, CH), 5.67 (m, 1H), 5.06–4.90 (m, 2H), 4.60 (d, *J* = 10.5 Hz, 1H, ArH–CH_aH_b), 4.44 (s, 2H, Ph–CH_2), 4.43 (d, *J* = 10.2 Hz, 1H, ArH–CH_aH_b), 3.78 (s, 3H, CH_3), 3.55 (dd, *J* = 4.9, 8.8 Hz, 1H, CH), 3.41 (dd, *J* = 6.6, 9.0 Hz, 1H, Ph–CH_2–O–CH_aH_b), 3.30 (dd, *J* = 4.7, 7.0 Hz, 1H, Ph–CH_2–O–CH_aH_b), 2.53 (s, 3H, S–CH_3), 2.24–2.09 (m, 3H, allylic-CH_2, CH), 2.02–1.80 (m, 2H, 2 × CH), 1.09 (d, *J* = 6.9 Hz, 3H, CH_3), 1.01 (d, *J* = 7.1 Hz, 3H, CH_3), 0.93 (d, *J* = 6.7 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.2, 158.9, 138.7, 136.3, 131.2, 129.0, 128.2, 127.4, 127.3, 116.6, 113.5, 86.8, 83.7, 73.9, 73.0, 72.2, 55.2, 38.3, 38.1, 36.9, 36.1, 18.7, 16.0, 14.7, 12.2; HRMS (ESI): $[M+Na]^+$ *m/z* calcd for $C_{29}H_{40}O_4NaS_2$: 539.2265, found: 539.2255 (−1.9907 ppm error).

4.1.9. (4*S*,6*S*,7*S*,8*R*)-9-(Benzyloxy)-7-[(4-methoxybenzyl)oxy]-4,6,8-trimethyl-1-nonene 15

A solution of **14** (9.2 g, 17.80 mmol), tributyltin hydride (23.90 mL, 98.02 mmol), and AIBN (0.175 g, 1.06 mmol) in toluene (130 mL) was heated at reflux for 1 h. The mixture was cooled, concentrated in vacuo, and purified by column chromatography (1:19, EtOAc/hexane) to afford **15** (6.65 g, 91%) as an oil. R_f = 0.65 (EtOAc/hexane, 1:19); $[\alpha]_D^{25} = +12.9$ (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 2959, 2921, 1612, 1512, 1457, 1367, 1301, 1247, 1173, 1083 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.28 (m, 5H, ArH), 7.14 (d, *J* = 8.0 Hz, 2H, ArH), 6.79 (d, *J* = 8.0 Hz, 2H, ArH), 5.72 (m, 1H), 5.08–4.88 (m, 2H), 4.45 (s, 2H, Ph–CH_2), 4.43 (ABq, *J* = 5.8, Hz, 2H, ArH–CH_2), 3.78 (s, 3H, CH_3), 3.49 (d, *J* = 5.1 Hz, 2H, CH_2), 3.16 (dd, *J* = 3.6, 7.3 Hz, 1H, CH), 2.20–1.20 (m, 7H), 1.01 (d, *J* = 7.3 Hz, 3H, CH_3), 0.97 (d, *J* = 6.6 Hz, 3H, CH_3), 0.89 (d, *J* = 5.8 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 138.7, 137.2, 131.3, 129.0, 128.2, 127.5, 127.3, 115.6, 113.6, 86.0, 74.4, 73.0, 72.7, 55.1, 39.8, 37.8, 36.3, 32.6, 30.1, 20.8, 17.6, 15.6; HRMS (ESI): $[M+Na]^+$ *m/z* calcd for $C_{27}H_{38}O_3Na$: 433.2718, found: 433.2709 (−2.2275 ppm error).

4.1.10. (2*R*,3*S*,4*S*,6*S*)-1-(Benzyloxy)-2,4,6-trimethyl-8-nonen-3-ol 16

To a solution of **15** (6.2 g, 15.11 mmol) in CH_2Cl_2:H_2O [10:1, 30 mL] was added dichlorodicyanoquinone (DDQ) (5.14 g, 22.67 mmol) at 0 °C. The solution was stirred for 2 h. After the reaction was completed, the solution was filtered through a pad of *Celite*. The *Celite* pad was washed with CH_2Cl_2 (3 × 50 mL). The combined filtrate was concentrated, and purification by column chromatography (1:4, EtOAc/hexane) provided **16** as a colorless liquid (3.9 g, 89%). R_f = 0.3 (EtOAc/hexane, 1:9); $[\alpha]_D^{25} = -25.0$ (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3482, 2959, 2922, 1455, 1219, 1088, 988 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, 5H, ArH), 5.75 (m, 1H), 5.11–4.89 (m, 2H), 4.50 (s, 2H, Ph–CH_2), 3.60 (dd, *J* = 3.6, 8.8 Hz, 1H, Ph–O–CH_aH_b), 3.43 (6.6, 8.8 Hz, 1H, Ph–O–CH_aH_b), 3.25 (m, 1H, CH),

3.10 (br s, 1H, OH), 2.15 (m, 1H, CH), 2.04–1.07 (m, 6H), 0.94 (d, J = 6.6 Hz, 3H, CH_3), 0.90 (d, J = 5.1 Hz, 3H, CH_3), 0.89 (d, J = 6.6 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6, 137.4, 128.4, 127.7, 127.6, 115.6, 81.3, 75.5, 73.5, 39.8, 36.8, 35.3, 33.0, 30.1, 21.0, 17.2, 14.2; HRMS (ESI): $[M+Na]^+$ m/z calcd for $C_{19}H_{30}O_2Na$: 313.2143, found: 313.2154 (+3.3517 ppm error).

4.1.11. (1*S*,2*S*,4*S*)-1-[(1*R*)-2-(Benzyloxy)-1-methylethyl]-2,4-dimethyl-6-heptenyl methylsulfanyl)methanethioate 17

To a solution of sodium hydride (0.65 g, 27.07 mmol) in anhydrous THF (20 mL), alcohol **16** (3.8 g, 13.1 mmol) in anhydrous THF (10 mL) was added at 0 °C and allowed to stir at room temperature for 0.5 h. To this reaction mixture, carbon disulfide (2.34 mL, 30.0 mmol) and iodomethane (1.61 mL, 20.0 mmol) were added at 0 °C. The mixture was stirred at room temperature for 2 h. After completion of the reaction at 0 °C, it was quenched by the slow addition of crushed ice. The mixture was raised to room temperature and separated, and the aqueous layer was washed with CH_2Cl_2 (2×50 mL). The combined organic extracts were dried (Na_2SO_4), concentrated in vacuo, and purified by column chromatography (1:14, EtOAc/hexane) to afford **17** (4.53 g, 91%) as a liquid. R_f = 0.42 (EtOAc/hexane, 1:12); $[\alpha]_D^{25} = +11.5$ (c 1.1, $CHCl_3$); IR (neat): ν_{max} 2963, 2923, 1455, 1375, 1223, 1098, 1049, 738, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 7.27 (m, 5H, ArH), 5.79–5.65 (m, 2H, db H, CH), 5.02–4.92 (m, 2H), 4.43 (s, 2H, Ph–CH_2), 3.49 (dd, J = 4.3, 9.0 Hz, 1H, Ph–O–CH_aH_b), 3.24 (dd, J = 6.9, 9.0 Hz, 1H, Ph–O–CH_aH_b), 2.53 (s, 3H, CSS–CH_3), 2.26 (m, 1H, CH), 2.08 (m, 2H, allylic-CH_2), 1.76 (m, 1H, CH), 1.59 (m, 1H, CH), 1.42 (m, 1H, aliphatic-CH_aH_b), 1.08 (m, 1H, aliphatic-CH_aH_b), 1.03 (d, J = 6.9 Hz, 3H, CH_3), 0.96 (d, J = 6.7 Hz, 3H, CH_3), 0.91 (d, J = 6.6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 216.5, 138.4, 136.8, 128.2, 127.5, 127.3, 115.9, 89.8, 73.1, 72.0, 39.7, 38.0, 35.8, 32.8, 30.0, 20.8, 18.7, 16.8, 14.9; HRMS (ESI): $[M+Na]^+$ m/z calcd for $C_{21}H_{32}O_2NaS_2$: 403.1741, found: 403.1723 (−4.5733 ppm error).

4.1.12. (4*S*,6*S*,8*S*)-9-(benzyloxy)-4,6,8-trimethyl-1-nonene 18

A solution of **17** (4.4 g, 17.80 mmol), tributyltin hydride (15.54 mL, 63.76 mmol), and AIBN (0.113 g, 0.69 mmol) in anhydrous toluene (75 mL) was heated at reflux for 1 h. The mixture was cooled, concentrated in vacuo, and purified by column chromatography (1:19, EtOAc/hexane) to afford **18** (2.91 g, 92%) as a colorless liquid. R_f = 0.43 (EtOAc/hexane, 1:19); $[\alpha]_D^{25} = +2.9$ (c 1.0, $CHCl_3$); IR (neat): ν_{max} 2956, 2915, 1455, 1372, 1102, 968, 736 cm^{-1}; ^{1}H NMR ($CDCl_3$ 200 MHz) δ 7.27 (m, 5H, ArH), 5.72 (m, 1H), 5.42–4.84 (m, 2H), 4.45 (s, 2H, Ar–CH_2), 3.23 (m, 2H, CH_2), 2.23–1.72 (m, 2H, CH_2), 1.68–1.12 (m, 5H), 1.01–0.87 (m, 2H, CH_2), 0.93 (d, J = 6.6 Hz, 3H, CH_3), 0.86 (d, J = 6.6 Hz, 3H, CH_3), 0.84 (d, J = 6.6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.8, 137.4, 128.2, 127.4, 127.3, 115.5, 75.9, 72.9, 44.5, 41.7, 40.8, 30.9, 29.9, 27.5, 20.8, 20.2, 18.3; HRMS (ESI): $[M+Na]^+$ m/z calcd for $C_{19}H_{30}ONa$: 297.2194, found: 297.2196 (+0.5533 ppm error).

4.1.13. (2*S*,4*S*,6*S*)-2,4,6-Trimethylnonan-1-ol 19

A stirred solution of **18** (2.8 g 10.21 mmol) and 10% Pd/C (75 mg) in anhydrous EtOAc (50 mL), was hydrogenated at 1 atm and room temperature for 4 h. The reaction mixture was filtered through a *Celite* pad and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/hexane, 1:30) giving **19** (1.67 g, 88%) as a colorless liquid. R_f = 0.26 (EtOAc/hexane, 1:19); $[\alpha]_D^{25} = +5.2$ (c 0.3, $CHCl_3$); IR (neat): ν_{max} 3376, 2957, 2919, 1460, 1037, 771 cm^{-1}; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 3.52 (dd, J = 4.5, 9.8 Hz, 1H, HO–CH_aH_b), 3.35 (dd, J = 6.7, 10.5 Hz, 1H, HO–CH_aH_b), 1.71 (m, 1H), 1.58 (m, 1H), 1.54–0.97 (m, 9H), 0.92 (d, J = 6.7 Hz, 3H, CH_3), 0.89 (t, J = 7.5 Hz, 3H, CH_3), 0.87 (d, J = 7.5 Hz, 3H, CH_3), 0.84 (d, J = 6.7 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 68.2, 45.1, 41.2, 38.7, 33.0, 29.7, 27.4, 20.9, 20.4, 19.9, 17.5, 14.4; MS(ESI): m/z = 204 $[M+NH_4]^+$.

4.1.14. (2*S*,4*S*,6*S*)-2,4,6-Trimethylnonanal 5

To an ice-cooled solution of 2-(iodooxy)benzoic acid (7.36 g, 27.27 mmol) in anhydrous DMSO (3.69 mL, 51.57 mmol) was added a solution of alcohol **19** (1.6 g, 8.60 mmol) in anhydrous CH_2Cl_2 (15 mL). The mixture was stirred at room temperature for 3 h and then filtered through a *Celite* pad and washed with Et_2O (2×10 mL). The combined organic filtrates were washed with H_2O (2×5 mL) and brine, dried over anhydrous Na_2SO_4 (1 g), and concentrated in vacuo. The crude product was purified by silica gel column chromatography using (EtOAc/hexane, 1:200) to afford aldehyde **5** (1.28 g, 81%) as a yellow liquid. R_f = 0.62 (EtOAc/hexane, 1:19); $[\alpha]_D^{25} = +6.2$ (c 0.26, $CHCl_3$); ^{1}H NMR ($CDCl_3$ 400 MHz) δ 9.57 (d, J = 2.4 Hz, 1H, CHO), 2.55 (m, 1H, CH), 1.78 (m, 1H, CH), 1.62–1.46 (m, 2H, CH, CH_aH_b), 1.39–1.32 (m, 1H, CH),1.32–0.92 (m, 6H, $3 \times CH_2$, CH_aH_b), 1.10 (d, J = 7.2 Hz, 3H, CH_3), 0.88 (d, J = 6.4 Hz, 3H, CH_3), 0.87 (t, J = 7.2 Hz, 3H, CH_3), 0.84 (d, J = 6.4 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.5, 45.1, 44.1, 38.9, 38.4, 29.7, 27.9, 20.4, 20.2, 19.9, 14.4, 14.3.

4.1.15. Siphonarienone, [(*E*,6*S*,8*S*,10*S*)-4,6,8,10-tetramethyl-4-tridecen-3-one] 2

To a solution of **5** (0.1 g, 0.543 mmol) in anhydrous benzene (8 mL) was added ethylcarbonylethylidenetriphenylphosphorane (0.27 g, 0.776 mmol). The mixture was maintained at 80 °C for 3 h, and then the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:30) to afford **2** (76.6 mg, 56%) as a colorless oil. R_f = 0.4 (100% hexane); $[\alpha]_D^{25} = +16.0$ (c 1.2, $CHCl_3$); IR (neat): ν_{max} 2958, 1672, 1459, 1376 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.33 (d, J = 9.5 Hz, 1H), 2.75–2.58 (m, 1H, CH), 2.67 (q, J = 7.3 Hz, 2H, CH_2), 1.80 (s, 3H, CH_3), 1.55–1.4 (m, 3H), 1.4–1.25 (m, 3H), 1.24–1.13 (m, 2H), 1.13–1.04 (m, 2H), 1.09 (t, J = 7.3 Hz, 3H, CH_3), 1.01 (d, J = 6.5 Hz, 3H, CH_3), 0.88 (t, J = 7.3 Hz, 3H, CH_3), 0.84 (d, J = 6.5 Hz, 3H, CH_3), 0.81 (d, J = 6.5 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.9, 148.3, 135.4, 45.6, 44.7, 39.3, 31.2, 30.4, 29.6, 28.3, 20.7, 20.5, 19.9, 19.9, 14.4, 11.5, 9.0; MS(ESI): m/z = 270 $[M+NH_4]^+$.

4.1.16. Ethyl (*E*,4*S*,6*S*,8*S*)-2,4,6,8-tetramethyl-2-undecenoate 4

To a solution of **5** (0.75 g, 0.14 mmol) in anhydrous benzene (30 mL) was added ethoxycarbonylethylidenetriphenylphosphorane (2.10 g, 5.82 mmol). The mixture was maintained at 80 °C for 3 h, and then the solvents were removed in vacuo. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:40) to afford **4** (0.88 g, 81%) as a colorless oil. R_f = 0.4 (100% hexane); $[\alpha]_D^{25} = +26.5$ (c 1, $CHCl_3$); IR (neat): ν_{max} 2958, 2924, 1713, 1268, 751 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.51 (dd, J = 1.1, 10.0 Hz, 1H), 4.19 (m, 2H, O–CH_2), 2.62 (m, 1H, CH), 1.86 (d, J = 1.3 Hz, 3H, CH_3), 1.54–1.02 (m, 10H), 1.30 (t, J = 6.9 Hz, 3H, CH_3), 0.99 (d, J = 6.6 Hz, 3H, CH_3), 0.88 (d, J = 6.7 Hz, 3H, CH_3), 0.83 (t, J = 6.4 Hz, 3H, CH_3), 0.81 (d, J = 6.6 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 148.2, 126.2, 60.3, 45.5, 44.3, 39.3, 30.8, 29.7, 29.6, 28.1, 20.6, 20.4, 19.9, 14.4, 14.2, 12.4; HRMS (ESI): $[M+Na]^+$ m/z calcd for $C_{17}H_{32}O_2Na$: 291.2300, found: 291.2312 (+4.1195 ppm error).

4.1.17. (*E*,4*S*,6*S*,8*S*)-2,4,6,8-Tetramethyl-2-undecen-1-ol 20

To a stirred solution of ester **4** (0.15 g, 0.56 mmol) in anhydrous CH_2Cl_2 (10 mL) was added DIBAL-H (0.80 mL, 1.4 M, 1.12 mmol in hexane) dropwise over a period of 5 min at −78 °C under N_2 atmosphere. After stirring for 2 h at room temperature anhydrous MeOH (1 mL) was added at 0 °C, and the mixture was allowed to warm to room temperature, saturated aqueous solution of sodium potassium tartarate (5 mL) was added, and the resulting mixture was stirred vigorously until the two layers were separated. The organic layer was separated and the aqueous layer was extracted with additional CH_2Cl_2 (3×10 mL). The combined organic layers

were washed with H_2O, brine solution, and dried over anhydrous Na_2SO_4 (0.5 g). Removal of the solvent in vacuo and purification by silica gel column chromatography using (EtOAc/hexane, 1:24) to afford the alcohol **20** (0.91 g, 72% yield) as a liquid. R_f = 0.31 (EtOAc/hexane, 1:4); $[\alpha]_D^{25} = +9.4$ (*c* 0.2, $CHCl_3$); IR (neat): ν_{max} 3355, 1457, 1158, 1011 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.13 (dd, *J* = 1.1, 9.4 Hz, 1H), 4.0 (s, 2H, CH_2), 2.50 (m, 1H, CH), 1.69 (d, *J* = 1.1 Hz, 3H, CH_3), 1.55–0.95 (m, 10H), 0.93 (d, *J* = 6.6 Hz, 3H, CH_3), 0.88 (t, *J* = 6.7 Hz, 3H, CH_3), 0.83 (d, *J* = 5.6 Hz, 3H, CH_3), 0.81 (d, *J* = 6.4 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.2, 133.1, 69.2, 45.6, 44.9, 39.3, 29.7, 29.6, 27.8, 21.7, 20.5, 20.1, 20.0, 14.4, 13.8; MS(ESI): *m/z* = 249 $[M+Na]^+$.

4.1.18. Siphonarienal [(*E*,4*S*,6*S*,8*S*)-2,4,6,8-tetramethyl-2-undecenal] 1

To an ice-cooled solution of 2-(iodooxy)benzoic acid (107 mg, 0.397 mmol) in anhydrous DMSO (0.11 mL, 1.58 mmol) was added a solution of alcohol **20** (60 mg, 0.265 mmol) in anhydrous CH_2Cl_2 (5 ml). The mixture was stirred at room temperature for 2 h, filtered through a *Celite* pad, and washed with Et_2O (2 × 5 mL). The combined organic filtrates were washed with H_2O (2 × 5 mL) and brine, dried over anhydrous Na_2SO_4 (300 mg), and concentrated in vacuo. The crude product was purified by silica gel column chromatography using (EtOAc/hexane, 1:30) to afford aldehyde **1** (42 mg, 72%) as a liquid. R_f = 0.3 (100% hexane); $[\alpha]_D^{25} = +16.5$ (*c* 1, $CHCl_3$); IR (neat): ν_{max} 2958, 2923, 1714, 1458, 1098 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.39 (s, 1H, -CHO), 6.2 (qd, *J* = 1.3, 10.0 Hz, 1H), 2.83 (m, 1H), 1.78 (d, *J* = 1.1 Hz, 3H), 1.54–0.92 (m, 10H), 1.05 (d, *J* = 6.6 Hz, 3H, CH_3), 0.88 (t, *J* = 6.7 Hz, 3H, CH_3), 0.84 (d, *J* = 6.4 Hz, 3H, CH_3), 0.81 (d, *J* = 6.6 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.6, 160.8, 138.0, 45.5, 44.2, 39.2, 31.2, 29.6, 28.2, 20.5, 20.3, 20.0, 19.9, 14.3, 9.3; MS(ESI): *m/z* = 242 $[M+NH_4]^+$.

4.1.19. *N*-1-Methoxy-*N*-1,2,4,6,8-pentamethyl-(*E*,4*S*,6*S*,8*S*)-2-undecenamide 21

To a stirred solution of ester **4** (0.220 g, 0.82 mmol) and hydroxylamine hydrochloride (0.24 g, 2.46 mmol) in anhydrous THF (10 mL) was added ^{i}PrMgCl (1.64 mL, 3.28 mmpl, 2 M solution in THF) at −20 °C and allowed to stir for 1 h. The reaction mixture was quenched by adding saturated aqueous NH_4Cl (5 mL) and washed with EtOAc (2 × 5 mL). The combined organic layer was dried over Na_2SO_4 (0.3 g), concentrated in vacuo, and purified by silica gel column chromatography (EtOAc/hexanes, 1:19) to give **21** (186 mg, 80%) as a liquid. R_f = 0.21 (EtOAc/hexane, 1:13); $[\alpha]_D^{25} = +12.0$ (*c* = 1, $CHCl_3$); IR (neat): ν_{max} 2923, 1624, 769 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.44 (qd, *J* = 1.7, 10.3 Hz, 1H), 3.38 (s, 3H, O–CH_3), 2.61 (m, 1H, CH), 1.88 (s, 3H, *N*-CH_3), 1.47 (m, 3H, CH_3), 1.37–0.93 (m, 10H), 0.99 (d, *J* = 6.7 Hz, 3H, CH_3), 0.88 (t, *J* = 6.7 Hz, 3H, CH_3), 0.86 (d, *J* = 6.7 Hz, 3H, CH_3), 0.82 (d, *J* = 6.7 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 141.7, 126.5, 45.6, 44.4, 39.1, 37.8, 30.2, 29.6, 29.5, 28.2, 28.8, 20.2, 20.1, 19.9, 14.3, 13.9; MS(ESI): *m/z* = 284 $[M+H]^+$.

4.1.20. Pectinatone, (4-hydroxy-3,5-dimethyl-6-[(*E*,3*S*,5*S*,7*S*)-1,3,5,7-tetramethyl-1-decenyl]-2*H*-2-pyranone) 3

A solution of **21** (140 mg, 0.494 mmol) in anhydrous THF (5 mL) was added dropwise to a freshly prepared 1 M solution of LDA (1.0 mL) in anhydrous THF at −20 °C and allowed to stir for 30 min at 0 °C, then a solution of **22** (0.234 g, 1.482 mmol) in anhydrous THF (5 mL) was added dropwise at 0 °C and allowed to stir for a further 30 min at the same temperature. The reaction mixture was quenched by adding saturated aqueous NH_4Cl (6 mL) at 0 °C and allowed to warm to rt. The aqueous layer was separated and washed with EtOAc (2 × 5 mL), the combined organic layer was dried over Na_2SO_4 (0.2 g) and concentrated in vacuo to afford crude compound **23** (408 mg) as a liquid. Without further purification, DBU was added (1.0 mL, 6.711 mmol) to a stirred solution of crude compound **23** in anhydrous toluene and refluxed for 4 h. Toluene was removed under reduced pressure, the residue was diluted with CH_2Cl_2 (10 mL) and washed with water (3 mL). The aqueous layer was again washed with CH_2Cl_2 (2 × 10 mL), the combined organic layer was dried over Na_2SO_4 (0.2 g), concentrated in vacuo, and purified by silica gel column chromatography (EtOAc/hexanes, 1:2) to give **1** (8.0 mg, 51% over two steps) as a solid. Mp = 126–128 °C; R_f = 0.3 (EtOAc/hexane, 7:13); $[\alpha]_D^{25} = +60.5$ (*c* 0.1, $CHCl_3$); IR (neat): ν_{max} 3203, 2923, 2858, 1655, 1456, 1375, 1226 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.36 (m, 1H, CH), 2.60 (m, 1H, CH), 2.03 (s, 3H, CH_3), 1.97 (s, 3H, CH_3), 1.87 (s, 3H, CH_3), 1.50 (m, 2H), 1.41–0.78 (m, 8H), 0.92 (t, 3H, *J* = 6.4 Hz, CH_3), 0.87 (d, 3H, *J* = 6.0 Hz, CH_3), 0.86 (d, 3H, *J* = 6.0 Hz, CH_3), 0.81 (d, 3H, *J* = 6.4 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 164.5, 159.7, 142.9, 126.2, 105.5, 98.6, 45.8, 44.8, 39.4, 30.5, 29.6, 28.3, 21.3, 20.2, 20.1, 19.9, 14.8, 14.4, 11.4, 8.4; MS(ESI): *m/z* = 352 $[M+NH_4]^+$.

Acknowledgment

P.G. thanks CSIR, New Delhi, for the award of Fellowship.

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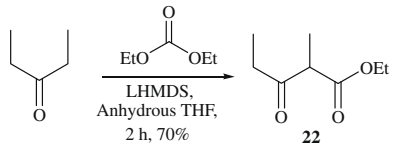
17. Compound **19** was prepared independently as follows:



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