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Stereoselective syntheses of siphonarienal and siphonarienone

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ABSTRACT

The asymmetric total synthesis of marine polypropionate natural products siphonarienal and siphonarienone has been achieved from a common precursor **3**. The key transformations of this synthesis are the diastereoselective oxidative kinetic resolution, Wittig olefination, Grignard reaction, and Evans asymmetric alkylation for the installation of a third stereogenic center of the target molecules from commercially available starting materials.

1. Introduction

Polypropionate containing natural products are an important class of biologically active molecules and efforts for the discovery of new strategies are still continuing. Siphonarienal **1**, siphonarienone **2**, and pectinatone can be isolated from the marine mollusks genus *Siphonaria*, such as *Siphonaria grisea* and *Siphonaria pectinate*, respectively (Fig. 1).[1] These compounds are active against Gram-positive bacteria, yeast, and various human cancer cell lines.[2] The structures of **1** and **2** were characterized by X-ray diffraction analysis and chemical correlations.[3] The members of this class of natural products contain a (2*S*,4*S*,6*S*)-trimethylnonane segment that is connected through an olefinic linker to a more polar oxygen containing group (Fig. 1).

However, many of the earlier syntheses of these compounds employed either iterative alkylation or a diastereoselective aldol reaction.[4] Other methods include the Zr-catalyzed asymmetric carboalumination,[5] iterative application of CuI-Tol-BINAP-catalyzed asymmetric conjugate addition,[6] Burgess's Ir-catalyzed hydrogenation,[7] and Feringa's Josiphos-catalyzed conjugate addition[8] by employing a desymmetrization strategy, which involves the asymmetric hydroboration of a known *meso*-olefin using (−)-IPC$_2$BH (diisopinocamphenyl-borane), PCC (=pyridinium chlorochromate), and Baeyer–Villiger oxidation reaction to set the stereochemistry of the trimethylnonyl unit,[9] and desymmetrization of *meso*-diol using Lipase-AK and vinyl acetate conditions.[10] However, herein we describe the utilization of a diastereoselective oxidative kinetic resolution using glucose oxidase from *Aspergillus niger* and an Evans asymmetric alkylation, which is an attractive method for the installation of methyl centers.

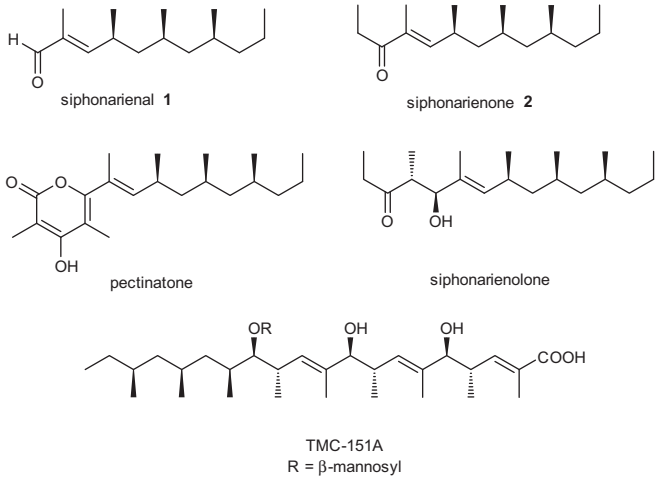

Figure 1. Representative examples of deoxypolypropionates.

2. Results and discussion

Our retrosynthetic plan for the synthesis of siphonarienal **1** and siphonarienone **2** is depicted in Scheme 1. The synthesis of **1** and **2** could be achieved by the functional group transformation of a key intermediate **3**. Compound **3** can be accessed from alcohol **13** via simple oxidation and Wittig olefination. Intermediate **13** was expected to be synthesized from **6** in a stereoselective manner involving a Wittig reaction, Evans asymmetric alkylation and Grignard reaction. Compound **6** can in turn be synthesized from the commercially available (*R*)-methyl 3-hydroxy-2-methyl propionate involving simple protection, oxidation and Wittig

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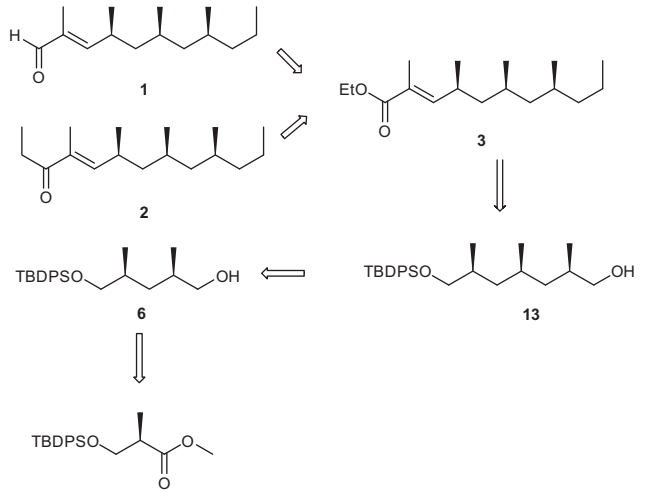


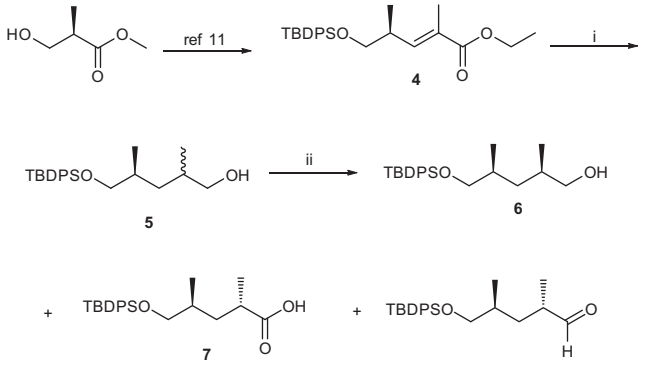
Scheme 1. Retrosynthetic analysis of siphonarienal **1** and siphonarienone **2**.

olefination, reduction, and diastereoselective oxidative kinetic resolution using glucose oxidase from *Aspergillus niger*.

The synthesis of siphonarienal **1** and siphonarienone **2** started from the known precursor **4**, which is available in three steps from the commercially available (*R*)-methyl 3-hydroxy-2-methylpropionate.[11] Ester **4** was transformed into alcohol **5** (as a 1:1 diastereomeric mixture) in 88% yield (Scheme 2).[12] In an earlier report, the selective oxidation of the alcohol was performed using whole cells *Gluconobacter oxydans*.[13] This procedure was cumbersome and requires a microbiologist to grow the cells, which are not commercially available. Since the reaction is apparently catalyzed by glucose oxidase, we performed the oxidation with commercially available glucose oxidase derived from *Aspergillus niger*. The oxidation proceeds selectively to give the aldehyde, which spontaneously oxidizes into carboxylic acid **7** during the reaction. At the end of the reaction, the desired alcohol **6** was obtained in 48% yield.

For our synthetic exercise, we required chiral precursor **6**. Therefore, the oxidation was stopped after a 2 h interval. Chiral alcohol **6** is known in the literature.[13a,14] and its absolute stereochemistry was confirmed by comparing its specific rotation with an authentic sample. The undesired acid **7** can be converted back into alcohol **5** using the literature procedure[13a] (Table 1).

Subsequent oxidation of alcohol **6** followed by chain elongation by C2 Wittig olefination with (ethoxycarbonylmethylene)triphenylphosphorane gave the α,β-unsaturated ester **8** in 86% yield



Scheme 2. Kinetic resolution of alcohol **5**. Reagents and conditions: (i) (a) Mg, MeOH, rt, 12 h; (b) LAH, Et_2O, 0–25 °C, 2 h; (ii) glucose oxidase, phosphate buffer pH = 8, DCM, 25 °C, 2 h.

Table 1
Product distribution in the oxidative kinetic resolution of alcohol **5** by glucose oxidase enzyme

Time (h)	Yield of alcohol **6**[a] (%)	Yield of acid **7** (%)	Yield of aldehyde (%)
1.0	35	30	10
2.0	48	46	<5
3.0	70	20	<5
5.0	80	17	Traces

[a] Yield refers to pure products after chromatography.

over two steps. Chemoselective reduction of the olefinic bond with Pd/C in EtOAc afforded the saturated ester **9** in 96% yield, which was then hydrolyzed under basic conditions to furnish the corresponding carboxylic acid **10** in 93% yield. The coupling of **10** with Evans' chiral oxazolidinone using pivaloyl chloride in the presence of Et_3N and LiCl gave the required compound **11** in 93% yield. Methylation of the Na-enolate of **11** with MeI gave the desired compound **12** with a diastereoselectivity of 97:3,[15] which was confirmed by ^1H NMR. Treatment of compound **12** with $NaBH_4$ in MeOH gave the chiral alcohol **13** in 92% yield with three stereogenic centers (Scheme 3). The primary alcohol **13** was converted into tosylate using TsCl, Et_3N followed by Grignard reaction with EtMgBr in THF at −20 °C in the presence of a catalytic amount of Li_2CuCl_4 to furnish product **14** in 85% yield.[16]

Deprotection of the silyl group in compound **14** using TBAF in THF gave the primary alcohol **15** in 95% yield. Oxidation of alcohol **15** provided the required aldehyde, which was then subjected to C3 Wittig olefination with (1-carbethoxyethylidene)-triphenylphosphorane to give the α,β-unsaturated ester **3** [(*E*)-isomer], as the major product in 88% yield over two steps,[17] which is a common precursor for the synthesis of two natural products **1** and **2**. Partial reduction of unsaturated ester **3** with DIBAL-H at −78 °C provided directly the target molecule siphonarienal **1**. For the synthesis of siphonarienone **2**, the α,β-unsaturated ester **3** was directly converted into the corresponding Weinreb amide using MeNHOMe·HCl and *i*-PrMgCl, which upon treatment with EtMgBr in THF provided the siphonarienone in 80% yield over two steps (Scheme 4). Spectroscopic data of both natural products **1** and **2** were in good agreement with those reported in the literature.[4d,6,9,18]

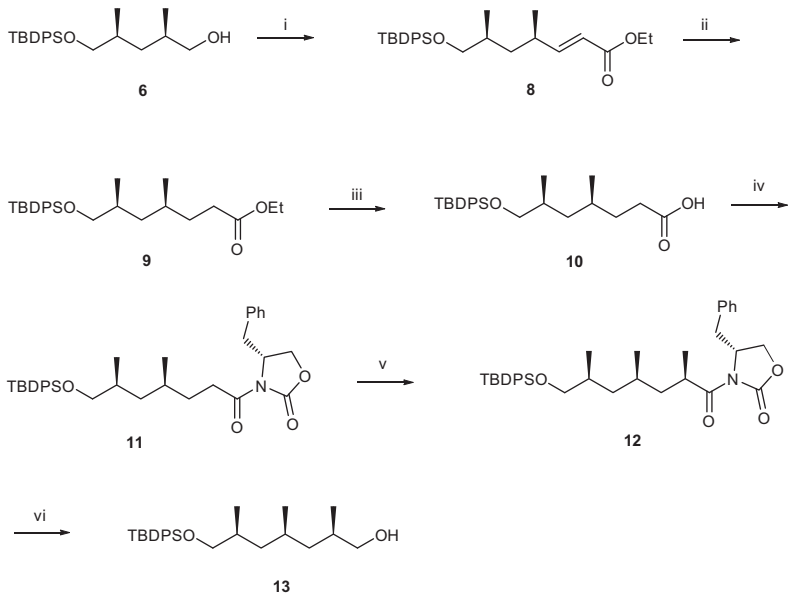
3. Conclusion

In conclusion we have demonstrated the asymmetric total syntheses of siphonarienal and siphonarienone from commercially available starting materials. The key transformations of these syntheses are the Wittig olefination, diastereoselective oxidative kinetic resolution using Glucose oxidase derived from *Aspergillus niger*, Evans asymmetric alkylation, and Grignard reaction. This approach further illustrates the application of oxidative kinetic resolution for the synthesis of deoxypolypropionate units. Further work is currently in progress to synthesize the other members of this family.

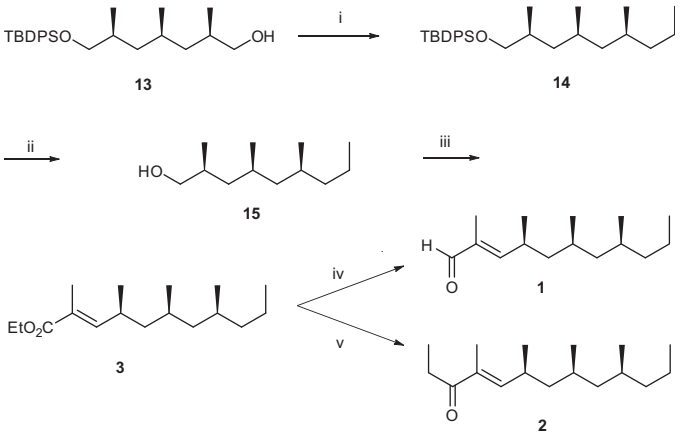
4. Experimental

4.1. General

Reagents and solvents were obtained from commercial sources and dried prior to use. Glucose Oxidase from *Aspergillus niger* was purchased from Sigma Aldrich. All reactions were performed in oven dried glassware under an inert atmosphere of nitrogen. All reactions were monitored by thin-layer chromatography (TLC) using UV light as visualizing agent and/or by exposure to Iodine



Scheme 3. Synthesis of alcohol **13**. Reagents and conditions: (i) (a) TPAP, NMO, CH_2Cl_2, 0.5 h; (b) Ph_3PCHCO_2Et, C_6H_6, 80 °C, 12 h; (ii) Pd/C, H_2, AcOEt, 2 h; (iii) $LiOH{\cdot}H_2O$, $MeOH/H_2O$ (4:1) 2 h; (iv) (*R*)-4-benzyl-oxazolidin-2-one, Piv-Cl, Et_3N, LiCl, THF, −20 to 0 °C, 3 h; (v) NaHMDS, MeI, −78 °C, THF; (vi) $NaBH_4$, MeOH, 0–25 °C.



Scheme 4. Synthesis of siphonarienal **1** and siphonarienone **2**. Reagents and conditions: (i) (a) TsCl, DCM, Et_3N, DMAP; (b) EtMgBr, Li_2CuCl_4, THF, −20 °C; (ii) TBAF, THF, 2 h; (iii) (a) TPAP, NMO, CH_2Cl_2, 0.5 h; (b) $Ph_3PC(Me)CO_2Et$, C_6H_6, 80 °C; (iv) DIBAL-H, CH_2Cl_2, −78 °C; (v) (a) MeNHOMe·HCl, *i*-PrMgCl, THF, −20 °C, 1.5 h; (b) EtMgBr, THF, rt, 45 min.

vapors and/or by spraying with *p*-anisaldehyde/H_2SO_4 reagent followed by heating at ca. 60 °C. Column chromatographic separations were carried out on silica gel (60–120 mesh) and flash chromatographic separations were carried out using 230–400 mesh silica gel using a mixture of ethyl acetate–hexane as eluent. Infrared spectra were recorded on Perkin–Elmer FT-IR 240-c spectrophotometer using KBr optics. NMR spectra were recorded in $CDCl_3$ on Bruker NMR instrument operating at ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz). Chemical shifts (δ) are quoted in parts per million and are internally referenced (0.0 ppm for TMS for ^1H NMR and 77.0 ppm for ^{13}C NMR). Coupling constants (J) are quoted in Hertz. The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, m = multiplet and br = broad. Mass spectra were recorded on Micromass VG-7070H for EI and VG Autospec M for FABMS. Optical rotations of the products were recorded on Digipol-781 M6U Polarimeter.

4.1.1. (*S*,*E*)-Ethyl 5-((*tert*-butyldiphenylsilyl)oxy)-2,4-dimethylpent-2-enoate 4

Compound **4** was synthesized by using the procedures reported in Ref. 11. $[\alpha]_D^{25} = -2.6$ (*c* 1.1, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.61–7.55 (m, 4H), 7.38–7.28 (m, 6H), 6.52 (dd, J = 1.4, 9.9 Hz, 1H), 4.15–4.07 (m, 2H), 3.50–3.45 (m, 2H), 2.71–2.63 (m, 1H), 1.73 (d, J = 1.4 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H), 0.97 (s, 9H), 0.96 (d, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.2, 144.4, 135.6, 133.6, 129.6, 127.6, 67.7, 60.4, 36.1, 26.8, 19.2, 16.3, 14.3, 12.6; IR (KBr): ν 3050, 2859, 2858, 1716, 1680, 1509, 1465, 1428, 1267, 1083, 740, 701 cm^{-1}; HRMS (*m*/*z*) calcd for $C_{25}H_{34}O_3NaSi$: 433.21694; found: 433.21747.

4.1.2. (2*R*,4*S*)-5-(*tert*-Butyldiphenylsilyl)oxy)-2,4-dimethylpental-1-ol 6

At first, magnesium turnings (2.92 g, 122.0 mmol) were added to the unsaturated ester **4** (5 gm, 12.2 mmol) in anhydrous MeOH (100 mL). Gas evolution was observed after 25 min of stirring and after four hours, all of the magnesium turnings were dissolved and a white precipitate had formed. Next, the reaction mixture was cooled to 0 °C and dilute HCl (200 mL, 2.5 M) was added to dissolve the solid, which was followed by extraction with diethyl ether (3 × 150 mL). The combined ether extracts were washed with sat. $NaHCO_3$ (50 mL) and brine (50 mL), then dried over $MgSO_4$ and concentrated in vacuo and purified on silica gel chromatography (EtOAc/Hexane, 1:19) of the crude product to afford a mixture of methyl and ethyl esters, which were taken up in anhydrous diethyl ether (30 mL) and reduced immediately with LAH (1.4 g, 36.6 mmol) in anhydrous ether (30 mL) at 0 °C. After 2 h of stirring, the mixture was diluted with ether (50 mL) and quenched by the slow addition of a saturated aq Na_2SO_4 solution (15 mL). When the effervescence subsided, the reaction mixture was filtered through a pad of Celite and washed with hot ethyl acetate (60 mL). The filtrate was evaporated in vacuo and the residue was purified by column chromatography (EtOAc/Hexane, 1:3) to furnish compound **5** (2 isomer, 3.97 g, 88% over 2 steps) as a colorless liquid. To a stirred solution of alcohol **5** (3.97 g, 10.74 mmol) in DCM (30 mL), phosphate buffer (25 ml, pH = 8, 0.1 M) and 800 mg of glucose oxidase enzyme were added at 25 °C. The biotransformations were monitored periodically by TLC analysis.

After two hours, the aqueous phase was extracted with DCM (3 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Column chromatographic separation on silica gel (Hexane/EtOAc, 3:1) afforded pure compound **6** (1.91 g, 48% yield). $[\alpha]_D^{25}$ = +1.75 (*c* 0.25, $CHCl_3$); Lit $[\alpha]_D^{25}$ = +1.8 (*c* 0.23, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.71–7.60 (m, 4H), 7.48–7.34 (m, 6H), 3.56–3.30 (m, 4H), 1.80–1.56 (m, 2H), 1.51–1.39 (m, 2H), 1.06 (s, 9H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$,75 MHz): δ 135.5, 133.8, 129.4, 127.5, 68.6, 67.9, 37.1, 32.9, 26.8, 17.8, 17.3; IR (KBr) ν 3455, 2931, 2856, 1110, 1091, 702 cm^{-1}; HRMS (*m*/*z*) calcd for $C_{23}H_{34}O_2NaSi$: 393.22203; found: 393.22189.

4.1.3. (4*R*,6*S*,*E*)-Ethyl 7-((*tert*-butyldiphenyl silyl)oxy)-4,6-dimethylhept-2-enoate 8

To a stirred solution of alcohol **6** (1.50 g, 4.05 mmol) and activated powder 4 Å molecular sieves (2 g) in anhydrous CH_2Cl_2 (40 ml) at 0 °C were added tetrapropylammonium perruthenate(VII), (70 mg, 0.2 mmol) and 4-methylmorpholine-*N*-oxide (700 mg, 6 mmol). The reaction mixture was stirred under argon for 30 min and filtered through a short pad of silica eluting with ethyl acetate to yield the aldehyde. To this crude aldehyde in benzene (20 mL) was added the stabilized ylide $Ph_3PCHCO_2CH_2CH_3$ (2.10 g, 6.0 mmol) and the reaction mixture was stirred overnight at 80 °C temperature. The reaction mixture was then concentrated under reduced pressure and purified on silica gel chromatography (EtOAc/Hexane, 1:19) to afford the unsaturated ester **8** (1.51 g, 86% over two steps) as a colorless liquid. $[\alpha]_D^{25}$ = +25.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.70–7.62 (m, 4H), 7.46–7.32 (m, 6H), 6.80 (dd, *J* = 15.7, 8.3 Hz, 1H), 5.78 (d, *J* = 15.7 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.50–3.40 (m, 2H), 2.46–2.30 (m, 1H), 1.74–1.48 (m, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.05 (s, 9H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.8, 154.4, 135.6, 133.9, 129.5, 119.7, 68.9, 60.1, 39.8, 34.1, 33.3, 26.8, 20.4, 19.2, 16.7, 14.2; IR (KBr): ν 2928, 2856, 1725, 1664, 1464, 1374, 1264, 1108, 1047, 821, 704, 506 cm^{-1}; HRMS (*m*/*z*) calcd for $C_{27}H_{38}O_3NaSi$: 461.24824; found: 461.24742.

4.1.4. (4*S*,6*S*)-Ethyl 7-((*tert*-butyldiphenylsilyl)oxy)-4,6-dimethylheptanoate 9

To a stirred solution of compound **8** (1.50 g, 3.42 mmol) in AcOEt (10 mL) was added Pd/C (10%, 20 mg) and subjected to hydrogenation under atmospheric pressure using H_2-filled balloon. The reaction was monitored by TLC. After complete consumption of the starting material, the reaction mixture was filtered through a pad of Celite and the filtrate was concentrated in vacuo and purified on silica gel chromatography (EtOAc/Hexane, 1:19) to afford the saturated ester **9** (1.44 g, 96% yield) as colorless liquid. $[\alpha]_D^{25}$ = +5.4 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.70–7.62 (m, 4H), 7.46–7.34 (m, 6H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.55–3.37 (m, 2H), 2.36–2.18 (m, 2H), 1.80–1.62 (m, 2H), 1.53–1.32 (m, 4H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.05 (s, 9H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.83 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 174.0, 135.6, 129.4, 127.5, 68.8, 60.1, 40.7, 33.0, 31.8, 31.5, 29.6, 26.8, 19.9, 17.5, 14.2; IR (KBr): ν 2928, 2856, 1738, 1464, 1430, 1372, 1254, 1107, 1054, 703, 612, 507 cm^{-1}; HRMS (*m*/*z*) calcd for $C_{27}H_{40}O_3NaSi$: 463.26389; found: 463.26295.

4.1.5. (4*S*,6*S*)-7-((*tert*-Butyldiphenylsilyl)oxy)-4,6-dimethylheptanoic acid 10

To a stirred solution of ester **9** (1.40 g, 3.18 mmol) in 25 mL of CH_3OH/H_2O (4:1) was added portion wise $LiOH{\cdot}H_2O$ (400 mg, 9.60 mmol) at 0 °C after which stirring was continued for 2 h at room temperature. The reaction mixture was then concentrated in vacuo and the residue was diluted with EtOAc (20 mL) and washed with saturated aq NH_4Cl solution and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Removal of solvent followed by column chromatography (EtOAc/hexane, 1:5) to afford the acid **10** (1.23 g, 93% yield) as a colorless liquid. $[\alpha]_D^{25}$ = +8.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.71–7.62 (m, 4H), 7.45–7.34 (m, 6H), 3.53–3.37 (m, 2H), 2.41–2.22 (m, 2H), 1.80–1.30 (m, 6H), 1.05 (s, 9H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 180.4, 135.6, 134.0, 129.8, 127.5, 68.8, 40.7, 33.1, 31.6, 31.3, 29.6, 26.9, 19.8, 19.3; IR (KBr): ν 2956, 2926, 2860, 1710, 1495, 1246, 1101, 912, 830, 768 cm^{-1}; HRMS (ESI): calcd for $C_{25}H_{36}O_3NaSi$: 435.23314; found 435.23238.

4.1.6. (*R*)-4-Benzyl-3-((4*S*,6*S*)-7-((*tert*-butyl diphenylsilyl)oxy)-4,6-dimethyl heptanoyl)oxazolidin-2-one 11

To a stirred solution of acid **10** (1.20 g, 2.91 mmol) in THF (15 mL) at −20 °C was added Et_3N (0.9 mL, 7.3 mmol) followed by PivCl (0.4 mL, 2.91 mmol) under a nitrogen atmosphere. After stirring for 1 h at −20 °C, LiCl (183 mg, 4.37 mmol) followed by (*R*)-1,3-oxazolidin-2-one (560 g, 3.2 mmol) were added at the same temperature. The stirring was continued for 1 h at −20 °C and then 2 h at 0 °C. It was then quenched with saturated NH_4Cl solution (10 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using ethyl acetate and hexane (1:16) to give **11** (1.54 g, 93%) as a pale yellow liquid. $[\alpha]_D^{25}$ = +40.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.71–7.63 (m, 4H), 7.45–7.16 (m, 11H), 4.72–4.60 (m, 1H), 4.24–4.11 (m, 2H), 3.91–3.83 (m, 1H), 3.52 (dd, *J* = 5.3, 9.6 Hz, 1H), 3.41 (dd, *J* = 6.6, 9.8 Hz, 1H), 3.29 (dd, *J* = 3.2, 13.4 Hz, 1H), 304–2.78 (m, 2H), 2.72 (dd, *J* = 9.6, 13.2 Hz, 1H), 1.86–1.33 (m, 4H), 1.30–1.21 (m, 2H), 1.05 (s, 9H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.6, 153.3, 135.6, 133.9, 129.4, 128.9, 127.5, 127.3, 68.8, 66.0, 55.1, 40.9, 37.8, 33.2, 33.0, 30.9, 29.6, 26.8, 19.9, 19.3, 17.6; IR (KBr): ν 2925, 2855, 1783, 1698, 1457, 1385, 1352, 1273, 1195, 1106, 770, 702 cm^{-1}; HRMS (ESI): calcd for $C_{35}H_{45}NO_4Si$ Na: 594.30101; found 594.29941.

4.1.7. (*R*)-4-Benzyl-3-((2*R*,4*R*,6*S*)-7-((*tert*-butyldiphenylsilyl)oxy)-2,4,6-trimethyl heptanoyl)oxazolidin-2-one 12

A flame dried 100 mL round bottom flask was charged with **11** (1.5 g, 2.63 mmol) and 25 mL anhydrous THF. The solution was cooled to −78 °C, NaHMDS (1 M solution in THF, 4.0 mL, 4.0 mmol) was added dropwise with stirring under a nitrogen atmosphere. After 30 min of stirring, MeI (0.33 mL, 5.26 mmol) was added dropwise to the reaction mixture and then stirring was continued for another 2 h at −78 °C. The mixture was then quenched with saturated NH_4Cl (15 mL), warmed to room temperature, and then extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using ethyl acetate and hexane (1:19) to afford product **12** (1.43 g, 93%) as colorless liquid. $[\alpha]_D^{25}$ = +42.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.71–7.62 (m, 4H), 7.45–7.18 (m, 11H), 4.67–4.60 (m, 1H), 4.14 (d, *J* = 5.3 Hz, 2H), 3.91–3.83 (m, 1H), 3.50 (dd, *J* = 5.3, 9.7 Hz, 1H), 3.41 (dd, *J* = 6.6, 9.6 Hz, 1H), 3.24 (dd, *J* = 3.2, 13.3 Hz, 1H), 2.75 (dd, *J* = 9.6, 13.5 Hz, 1H), 1.95–1.77 (m, 3H), 1.50–1.32 (m, 3H), 1.20 (d, *J* = 6.7 Hz, 3H), 1.05 (s, 9H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.83 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 177.2, 152.9, 135.6, 134.0, 129.4, 128.8, 127.5, 127.3, 69.1, 65.9, 55.2, 41.5, 40.5, 37.8, 35.3, 33.0, 29.7, 28.1, 26.8, 20.5, 19.3, 18.7, 17.6; IR (KBr): ν 2957, 2923, 2853, 1783, 1699, 1460, 1385, 1351, 1218,

1109, 772, 703, 613 cm^{-1}; HRMS (ESI): calcd for $C_{36}H_{47}NO_4SiNa$: 608.31666; found 608.31370.

4.1.8. (2*R*,4*S*,6*S*)-7-((*tert*-Butyldiphenylsilyl)oxy)-2,4,6-trimethylheptan-1-ol 13

To a stirred solution of **12** (1.4 g, 2.4 mmol) in MeOH (10 mL) was added $NaBH_4$ portionwise (274 mg, 7.2 mmol) at 0 °C. The reaction mixture was allowed to stir for 1 h at the same temperature and then quenched with saturated aqueous NH_4Cl. The solvent was removed under reduced pressure and the resulting residue was diluted with water and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure, after which the crude product was purified by silica gel column chromatography (EtOAc/hexane, 1:9) to afford pure product **13** (910 mg, 92%) as a viscous liquid. $[\alpha]_D^{25} = -6.0$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.70–7.63 (m, 4H), 7.45–7.34 (m, 6H), 3.54–3.45 (m, 2H), 3.44–3.30 (m, 2H), 1.79–1.64 (m, 2H), 1.41–1.18 (m, 5H), 1.05 (s, 9H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.4 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 135.6, 134.0, 129.5, 127.6, 68.7, 68.2, 41.8, 41.2, 33.2, 27.7, 26.9, 21.0, 18.1, 17.6, 16.5. IR (KBr): *v* 3019, 2957, 2928, 2857, 1466, 1428, 1364, 1216, 1109, 1033, 823, 771, 667 cm^{-1}. HRMS (ESI): calcd for $C_{26}H_{40}O_2SiNa$: 435.26898; found 435.27008.

4.1.9. *tert*-Butyldiphenyl(((2*S*,4*S*,6*S*)-2,4,6-trimethylnonyl)oxy) silane 14

A solution of alcohol **13** (0.9 g, 2.18 mmol) in dry CH_2Cl_2 (15 mL) and dry triethylamine (0.4 mL, 2.6 mmol) was cooled at 0 °C, after which was added *p*-toluenesulfonyl chloride (414 mg, 2.18 mmol). The resulting mixture was stirred at room temperature for 3 h. After complete conversion as confirmed by TLC, the mixture was quenched with NH_4Cl solution and then extracted with EtOAc (3 × 15 mL). Removal of the solvent followed by purification on silica gel column chromatography (ethyl acetate/hexane, 1:19) gave the pure tosyl derivative. To a stirred solution of activated Mg-turnings (178 mg, 7.4 mmol) in anhydrous diethyl ether (6 mL), ethyl bromide (0.6 mL, 7.63 mmol) was added slowly. After the complete addition, the mixture was then heated at reflux (~30 min) until initiation of the reaction. After disappearance of the metal, this solution was transferred via a cannula to a solution containing tosylate (1.166 g, 2.06 mmol) in dry diethyl ether (20 mL) at −20 °C under a nitrogen atmosphere. To this mixture, a solution of Li_2CuCl_4 (0.1 M in tetrahydrofuran, 0.2 mL, 0.2 mmol) was slowly added. The resulting mixture was stirred vigorously overnight at room temperature and then quenched with saturated aqueous NH_4Cl (10 mL) at 0 °C and then extracted with diethyl ether (3 × 20 mL). Removal of the solvent under reduced pressure followed by column chromatography (Pentane:Et_2O, 5:1) gave product **14** as a colorless liquid (786 mg, 85% yield). $[\alpha]_D^{25} = -7.0$ (*c* 1.07, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.68–7.54 (m, 4H), 7.40–7.25 (m, 6H), 3.45–3.29 (m, 2H), 1.85–1.75 (m, 1H), 1.72–1.60 (m, 2H), 1.44–1.09 (m, 6H), 0.98 (s, 9H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.89–0.84 (m, 5H), 0.82 (d, *J* = 6.6 Hz, 3H), 0.76 (d, *J* = 6.3 Hz, 3H) ^{13}C NMR ($CDCl_3$, 75 MHz): δ 135.6, 134.0, 129.5, 127.5, 69.4, 43.2, 41.3, 40.4, 33.1, 32.4, 32.2, 27.5, 27.3, 26.9, 20.6, 19.9, 19.7, 19.3, 17.8, 16.6. IR (KBr): *v* 2958, 2928, 2857, 1464, 1428, 1380, 1363, 1219, 1110, 824, 772, 703, 614 cm^{-1}. HRMS (ESI): calcd for $C_{28}H_{45}OSi$: 425.32396; found 425.32340.

4.1.10. (2*S*,4*S*,6*S*)-2,4,6-Trimethylnonan-1-ol 15

To a stirred solution of **14** (750 mg, 1.77 mmol) in dry THF (15 mL), was added TBAF (1 M solution in THF, 5.3 mL, 5.3 mmol) under a nitrogen atmosphere. The resulting reaction mixture was stirred for 5 h and then concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using ethyl acetate/hexane mixture (1:9) to yield compound **15** (313 mg, 95% yield) as a colorless oil. $[\alpha]_D^{25} = -12.0$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 3.50 (dd, *J* = 5.3, 10.6 Hz, 1H), 3.34 (dd, *J* = 6.8, 10.6 Hz, 1H), 1.78–1.64 (m, 2H), 1.62–1.43 (m, 2H), 1.40–1.10 (m, 6H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.90–0.82 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 68.2, 45.1, 41.2, 38.8, 33.0, 29.7, 27.5, 20.9, 20.4, 19.9, 17.5, 14.4; IR (KBr): *v* 3449, 2955, 2919, 2857, 1637, 1457, 1371, 1101, 760 cm^{-1}. HRMS (ESI): calcd for $C_{12}H_{26}ONa$: 209.18813; found 209.18890.

4.1.11. (4*S*,6*S*,8*S*,*E*)-Ethyl 2,4,6,8-tetramethyl undec-2-enoate 3

To a stirred solution of alcohol **15** (300 mg, 1.61 mmol) and activated powder 4 Å molecular sieves (800 mg) in anhydrous CH_2Cl_2 (15 ml) at 0 °C were added tetrapropyl ammonium perruthenate(VII), (28 mg, 0.08 mmol) and 4-methylmorpholine-*N*-oxide (283 mg, 2.4 mmol). The mixture was stirred under argon for 30 min and then filtered through a short pad of silica eluting with ethyl acetate to yield the aldehyde. To this crude aldehyde in benzene (10 mL) was added the stabilized ylide $Ph_3PC(Me)CO_2CH_2CH_3$ [(1-carbethoxyethylidene)-triphenylphosphorane] (875 mg, 2.14 mmol) and resulting mixture was stirred overnight at 80 °C. The reaction mixture was concentrated under reduced pressure and purified on silica gel chromatography (3% EtOAc/hexane) to afford the unsaturated ester **3** (378 mg, 88% over two steps) as a colorless liquid. $[\alpha]_D^{25} = +18.1$ (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 6.45 (d, *J* = 10.2 Hz, 1H) 4.28–4.11 (m, 2H), 2.68–2.53 (m, 1H), 1.84 (s, 3H), 1.54–1.14 (m, 10H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.88 (t, *J* = 6.8 Hz, 3H), 0.86–0.76 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.3, 148.0, 126.2, 60.2, 45.5, 44.3, 39.3, 30.8, 29.6, 28.1, 20.5, 20.4, 19.9, 14.3, 14.2, 12.4; IR (KBr): *v* 3453, 2958, 2925, 1711, 1648, 1460, 1378, 1102, 1035, 760, 667 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{32}O_2$ 268.23968; found 268.23968.

4.1.12. (4*S*,6*S*,8*S*,*E*)-2,4,6,8-Tetramethyl-2-undecenal (siphonarienal) 1

To a cooled (−78 °C) solution of **3** (185 mg, 0.69 mmol) in dry CH_2Cl_2 (5 mL), DIBAL-H (0.75 mL, 0.75 mmol, 20% solution in toluene) was added slowly. The resulting mixture was allowed to stir for 30 min at −78 °C. The reaction was quenched with sat. solution of sodium potassium tartarate (5 mL). The reaction mixture was then stirred vigorously at room temperature until a clear biphasic separation was observed. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were concentrated in vacuo. Purification of the residue by column chromatography (EtOAc/hexane, 1:30) gave siphonarienal **1** (247 mg, 80%) as a colorless liquid. $[\alpha]_D^{25} = +16.1$ (*c* 1.1, $CHCl_3$). Lit. $[\alpha]_D^{30} = +16.5$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 9.39 (s, 1H), 6.23 (d, *J* = 9.8 Hz, 1H), 2.92–2.75 (m, 1H), 1.77 (s, 3H), 1.55–1.10 (m, 7H), 1.05 (d, *J* = 6.0 Hz, 3H), 0.95–0.77 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 195.5, 160.7, 137.9, 45.6, 44.2, 39.2, 32.2, 29.6, 28.2, 20.5, 20.3, 20.0, 19.9, 14.3, 9.3; IR (neat): *v* 2956, 2925, 2910, 2871, 2705, 1691, 1644, 1457, 1378, 1008, 807 cm^{-1}; MS (ESI): *m*/*z* = 225 $(M+H)^+$.

4.1.13. [(6*S*,8*S*,10*S*,*E*)-4,6,8,10-Tetramethyl tridec-4-3-one] (siphonarienone) 2

To a stirred solution of **3** (185 mg, 0.69 mmol) and *N*,*O*-dimethylhydroxylamine·hydrochloride (MeONHMe·HCl) (202 mg, 2.07 mmol) in dry THF (5 mL) at −20 °C was added ^iPrMgCl solution (2 M solution in THF, 1.15 mL, 3.0 mmol) slowly. After 1.5 h, the reaction was quenched satd NH_4Cl solution and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. Without further purification, a solution of Weinreb amide containing residue was used

for the next step. To a stirred solution of this in dry THF (5 mL) was added EtMgBr (3 M solution in Et_2O, 1.15 mL, 3.45 mmol) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 45 min at room temperature. After completion of the reaction, it was quenched with satd NH_4Cl solution. The aqueous layer was extracted with Et_2O (3×10 mL), and the combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The resulting residue was purified by column chromatography (ethyl acetate/hexane, 1:30) gave the siphonarienone (**2**) (139 mg, 80%) as a colorless oil. $[\alpha]_D^{25}$ = +22.4 (*c* 1.0, $CHCl_3$); Lit. $[\alpha]_D^{30}$ = +26.4 (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 6.34 (dd, J = 9.6, 1.2 Hz, 1H), 2.75–2.64 (m, 3H), 1.80 (s, 3H), 1.54–1.15 (m, 10H), 1.10 (t, J = 7.3 Hz, 3H), 1.0 (d, J = 6.6 Hz, 3H), 0.87 (t, J = 7.2 Hz, 3H), 0.83 (d, J = 6.4 Hz, 3H), 0.81 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 202.8, 148.2, 135.3, 45.5, 44.5, 39.3, 31.2, 30.3, 29.6, 28.2, 20.7, 20.4, 19.9, 14.4, 11.5, 8.9; IR (neat): ν 3451, 2960, 2940, 2871, 2844, 1700, 1650, 1450, 1360, 1250, 1050, 790 cm^{-1}; MS (ESI): m/z = 253 $(M+H)^+$.

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