Divergent Enantioselective Total Synthesis of Siphonarienal, Siphonarienone, and Pectinatone

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A divergent synthesis of siphonarienal, siphonarienone, and pectinatone has been achieved from a common precursor **4**, which was synthesized by using an enzymatic desymmetrization approach. The major key steps involved were *Grignard* reaction, *Wittig* reaction, *Evans*' asymmetric alkylation, and base-catalyzed cyclization.

Introduction. – The siphonarienes belong to a class of polypropionates [1], which includes polyether antibiotics [2] and macrolides [3]. Of these, deoxypropionate is a common recurring motif in many deoxygenated polyketide-type natural products [4]. A *syn*/*syn*-deoxypropionate unit is found in many natural products, *e.g.*, TMC-151A [5], pectinatone [6], and siphonarienes (and its congeners) [7]. The siphonarienes **1**, **2**, and pectinatone (**3**; *Fig.*) are marine polypropionate natural products and were isolated from the genus *Siphonaria* such as *Siphonariea grisea* [8] and *S. pectinata* [6a], respectively.

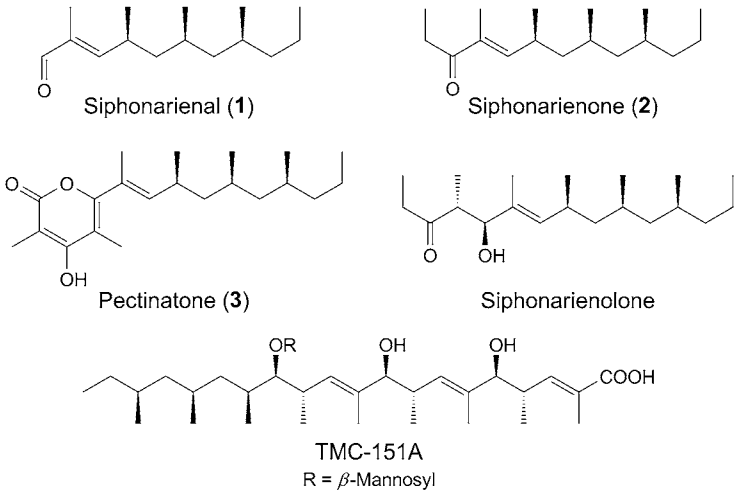


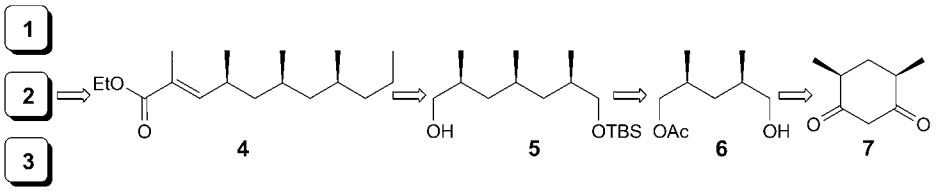
Figure. *Representative structures of deoxypolypropionate-containing natural products*

The polydeoxypropionates are known to exhibit various biological activities. They are active against *Gram*-positive bacteria *(Staphylococcus aureus* and *Bacillus subtilis*), yeast (*Candida albicaans* and *Sacchoromyces cervisiae*), and several human cancer cell lines [6b][9]. The structures of **1** [8], **2** [7a], and **3** [6b] were established on the basis of their spectroscopic data. Furthermore, the structure of **3** was confirmed by X-ray diffraction analysis [10].

In earlier studies, for the installation of new Me-bearing stereogenic centers mainly iterative alkylations or diastereoselective aldol reactions were used [11]. Other methods for the introduction of a Me group involved chiral auxiliaries [8][12], allylic substitutions [13], or substrate-controlled methods. Catalytic asymmetric methods have also been employed for the generation of stereogenic centers bearing a Me group, which include *Negishi*'s Zr-catalyzed carboalumination [7b], *Burgess*'s Ir-catalyzed hydrogenation [14], and *Feringa*'s Josiphos-catalyzed conjugate addition [15]. Of these, conjugate addition of MeMgBr to a commercially available α,β-unsaturated ester is one of the most direct entries into these structural elements. Recently, the total synthesis of the marine polypropionates siphonarienal (**1**), siphonarienone (**2**), and pectinatone (**3**) has been reported by our group by employing a desymmetrization strategy, *i.e.*, asymmetric hydroboration of the known *meso*-olefin using (−)-IPC_2BH (= diisopinocamphenylborane), PCC (= pyridinium chlorochromate), and *Baeyer–Villiger* oxidation reactions [7c]. Herein, we report an enantioselective total synthesis of **1**, **2**, and **3** by using enzymatic desymmetrization of a *meso*-diol and *Evans*' alkylation protocol.

Results and Discussion. – Retrosynthetically, we envisaged that the target molecules **1**–**3** could be synthesized from a common chiral precursor **4**. The latter was then proposed to be synthesized from **5** in two steps involving oxidation and C_3-homologation reactions. The intermediate **5** was assumed to be prepared from **6** in a stereoselective manner involving *Wittig* reaction and *Evans*' asymmetric alkylation. The key intermediate **6** was obtained from diketone **7** by $NaIO_4$ oxidation and $LiAlH_4$ reduction, followed by enzymatic desymmetrization (*Scheme 1*).

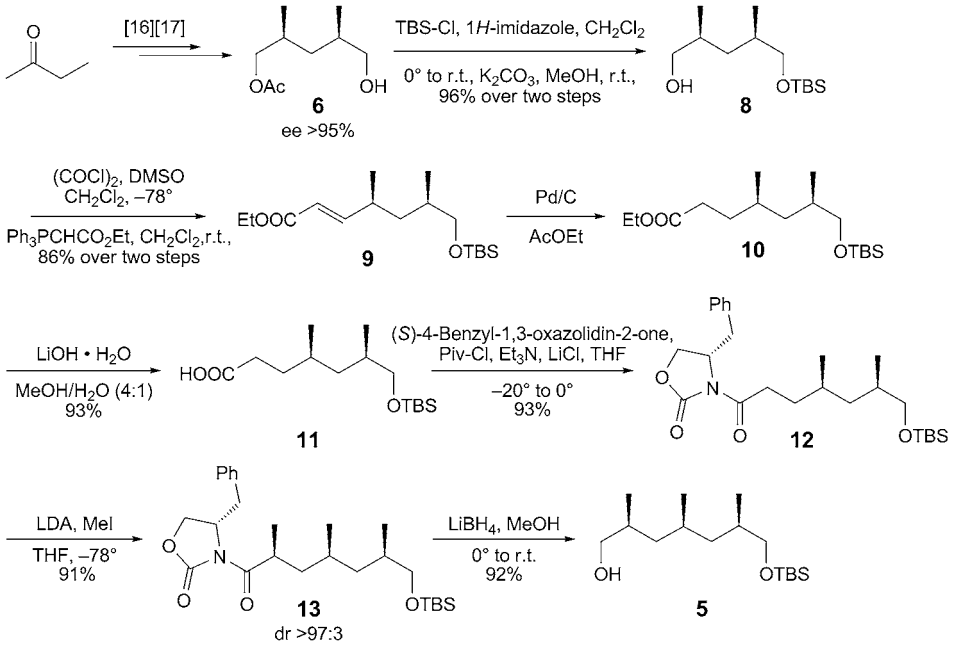
Scheme 1. *Retrosynthetic Analysis of Siphonarienal* (**1**), *Siphonarienone* (**2**), *and Pectinatone* (**3**). TBS = ^{t}BuMe$_2$Si.



Accordingly, we started our synthesis from *cis*-4,6-dimethylcyclohexan-1,3-dione (**7**), which was obtained by the condensation of methyl methacrylate with butan-2-one in the presence of MeONa [16a]. Thus obtained 1,3-dione was then converted to the corresponding diacid by means of periodate oxidation [16b]. Reduction of the diacid with $LiAlH_4$ in THF at 0° gave the *meso*-diol in 98% yield. Desymmetrization of the latter using Lipase-AK and vinyl acetate (as acylating agent) in THF at ambient

conditions [17] gave the mono acetate **6** in 74% yield with >95% ee along with the *meso*-diacetate, which was again converted to *meso*-diol using K_2CO_3 in MeOH. The mono acetate **6** was protected as its silyl ether using ^{t}BuMe$_2$SiCl (TBS-Cl) and 1*H*-imidazole in CH_2Cl_2 and then treated with K_2CO_3 in MeOH to furnish the desired terminal alcohol **8**. Subsequent oxidation of **8**, followed by elongation by C_2 using *Wittig* reaction gave the α,β-unsaturated ester **9** in 86% yield over two steps. Chemoselective reduction of the C=C bond with Pd/C in AcOEt afforded the saturated ester **10** in 96% yield, which was then subjected to hydrolysis under basic conditions to furnish the corresponding carboxylic acid **11** in 93% yield. The coupling of the latter with *Evans*' chiral oxazolidinone using pivaloyl chloride in the presence of Et_3N and LiCl gave the required compound **12** in 93% yield [18]. Diastereoselective methylation of the Li-enolate of **12** was achieved with MeI using a freshly prepared LDA (1.0M) to furnish the desired compound **13** with a diastereoselectivity of >97:3 [18c], which was confirmed by ^{1}H-NMR. Reduction of **13** with $LiBH_4$ in MeOH gave the primary alcohol **5** in 92% yield with three stereogenic centers (*Scheme 2*).

Scheme 2. *Synthesis of Alcohol* **5**. TBS = ^{t}BuMe$_2$Si; Piv-Cl = 2,2-Dimethylpropanoyl chloride; LDA = LiN^{i}Pr$_2$.

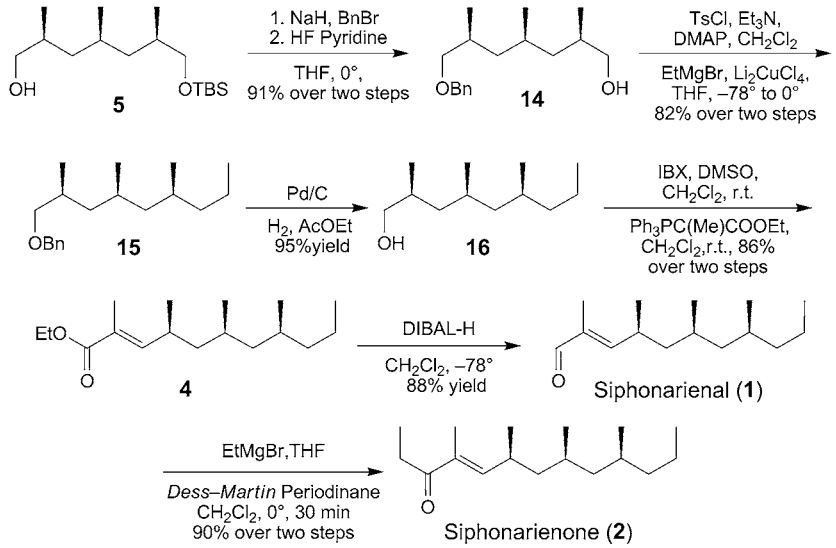


The alcohol **5** was then protected as its Bn derivative using NaH and BnBr in the presence of a catalytic amount of Bu_4NI (TBAI), followed by removal of the silyl group using HF-pyridine in THF to give the alcohol **14**. Tosylation of **14** with TsCl in the presence of Et_3N in dry CH_2Cl_2, at 0°, followed by *Grignard* reaction [17b] with EtMgBr in dry Et_2O at −20° in the presence of a catalytic amount of Li_2CuCl_4,

furnished the *Grignard* product **15** in 82% yield. Removal of the Bn group of **15** with Pd/C in AcOEt under H_2 afforded the primary alcohol **16** in good yield. *Swern* oxidation of **16** gave the required aldehyde, which was then subjected to C_3 *Wittig* reaction to afford the α,β-unsaturated ester **4** ((*E*)-isomer), as the major product in 86% yield over two steps [19], which was the common precursor for the synthesis of all the three natural products **1**, **2**, and **3**.

The target molecule, siphonarienal (**1**) was readily achieved in 88% yield by the partial reduction of **4** with DIBAL-H at $-78°$. *Grignard* reaction of **1** with EtMgBr followed by oxidation with *Dess–Martin* periodinane gave the siphonarienone (**2**) in 85% yield over two steps (isomeric purity was 99%; *Scheme 3*). The spectroscopic data of **1** and **2** were in good agreement with those reported [8][20].

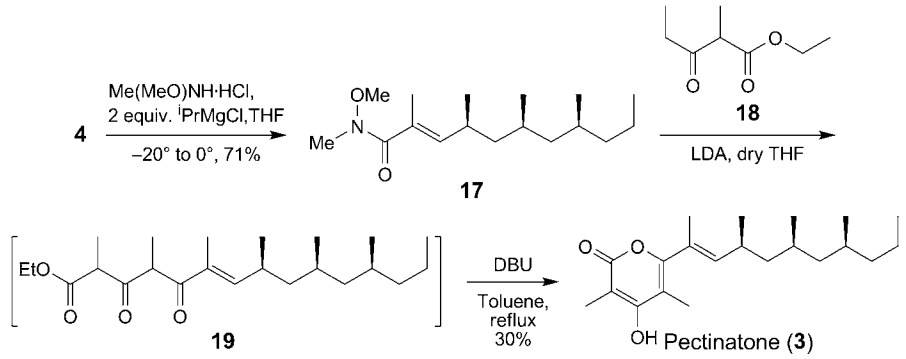
Scheme 3. *Synthesis of Siphonarienal* (**1**) *and Siphonarienone* (**2**). DMAP = 4-(Dimethylamino)pyridine; DIBAL-H = diisobutylaluminium hydride.



To achieve the synthesis of our next target molecule **3**, the ester **4** was treated with (methoxy)(methyl)ammonium chloride and ^{i}PrMgCl in THF at -20 to $0°$ to afford the *Weinreb* amide **17** in 71% yield. Treatment of the latter with ethyl 2-methyl-3-oxopentanoate (**18**; prepared by treating pentan-3-one with $(EtO)_2CO$ in the presence of LiHMDS (lithium bis(trimethylsilyl)amide) in dry THF), followed by base-catalyzed cyclization of the resulting β,δ-diketo ester **19** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) under refluxing toluene [21], gave pectinatone (**3**) in 30% yield (*Scheme 4*).

In summary, we have developed a highly enantioselective, divergent total synthesis of siphonarienal (**1**), siphonarinone (**2**), and pectinatone (**3**). This approach involves a lower number of steps in comparison with our earlier approach [7c]. The present synthesis includes an enzymatic desymmetrization of a *meso*-diol, *Wittig* olefination, *Evans*' asymmetric alkylation, and base-catalyzed cyclization as key steps.

Scheme 4. *Synthesis of Pectinatone* (**3**). DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene.



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Experimental Part

General. All reactions were performed under Ar. All glassware used for reactions are oven/flame-dried. Anh. solvents were distilled prior to use: THF from Na and benzophenone; CH_2Cl_2 and DMSO from CaH_2; and MeOH from Mg cake. Commercial reagents were used without purification. Column chromatography (CC): silica gel (60–120 mesh), unless otherwise mentioned. Anal. TLC: silica gel *60F254* pre-coated plates (250 mm thickness). Optical rotations: *Perkin-Elmer 343* polarimeter; in 10^{-1} Deg cm^2 g^{-1}. IR Spectra: *Perkin-Elmer Infrared-683* spectrometer; in $CHCl_3$ or KBr; $\tilde{\nu}$ in cm^{-1}. NMR Spectra: *Varian Gemini 200*, *Varian Unity 400*, *Varian Inova 500*, or *Bruker Avance 300* spectrometers; at 300, 400, and 500 MHz (^{1}H), and 75 MHz (^{13}C); in $CDCl_3$ soln., unless otherwise mentioned, chemical shifts (δ) in ppm downfield from Me_4Si; coupling constants (J) in Hz. ESI- or HR-ESI-MS: *Finnigan MAT 1020B* or *Micro Mass 70–70H* spectrometers; at 70 eV; m/z (rel. %).

(2S,4R)-5-Hydroxy-2,4-dimethylpentyl Acetate (**6**). A stirred soln. of *meso*-2,4-dimethylpentane-1,5-diol (4.0 g, 30.3 mmol, 1.0 equiv.) in THF (40 ml) was cooled to 0°. At this temp., *Amano Lipase AK* (220 mg) and vinyl acetate (4.20 ml, 3.90 g, 45.4 mmol, 1.50 equiv.) were added. The mixture was stirred for 30 min at 0° and 7 h at 5°. The enzyme was removed by suction filtration through *Celite*. The residue was further washed with Et_2O (2 × 30 ml) and dried (Na_2SO_4). The homogeneous filtrate was concentrated *in vacuo* and purified by CC (AcOEt/hexane 1:5) to afford **6** (3.902 g, 74%). Colorless oil. $[\alpha]_D^{25} = +10.5$ (c = 1.2, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): 3.97 (*dd*, J = 10.5, 5.2, 1 H); 3.85 (*dd*, J = 10.5, 6.7, 1 H); 3.49 (*dd*, J = 10.5, 6.0, 1 H); 3.42 (*dd*, J = 10.5, 6.0, 1 H); 2.05 (*s*, 3 H); 1.82–1.96 (*m*, 1 H); 1.64–1.78 (*m*, 1 H); 1.43 (br. *s*, 1 H); 1.39–1.49 (*m*, 1 H); 1.15–1.30 (*m*, 1 H); 0.96 (*d*, J = 6.7, 3 H); 0.95 (*d*, J = 6.7, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 171.3; 69.1; 67.9; 37.2; 32.9; 29.9; 20.9; 17.8; 17.2.

*(2S,4R)-5-[[(*tert*-Butyl)(dimethyl)silyl]oxy]-2,4-dimethylpentan-1-ol* (**8**). To a cold (0°) soln. of **6** (6.0 g, 34.4 mmol) in dry CH_2Cl_2 (80 ml) were added 1*H*-imidazole (4.69 g, 68.9 mmol) and TBS-Cl (6.20 g, 41.32 mmol). The resulting mixture was stirred at r.t. for 3 h. After completion of the reaction (TLC), the reaction was quenched with sat. aq. NH_4Cl, and the mixture was extracted with CH_2Cl_2 (3 × 50 ml). The combined org. layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to furnish the crude acetate. To the above mixture in MeOH (80 ml), K_2CO_3 (9.5 g, 68.0 mmol) was added at r.t. The mixture was stirred for 1 h at r.t. and then concentrated under reduced pressure. The residue was treated with sat. NH_4Cl and extracted with AcOEt (3 × 100 ml). The combined org. layers were washed with H_2O, brine, dried (Na_2SO_4), and concentrated in *vacuo*. The resulting crude product was purified by CC (AcOEt/hexane 1:9) to give **8** (8.143 g, 96%). Colorless oil. $[\alpha]_D^{25} = +0.9$ (c = 1.2, $CHCl_3$). IR (KBr): 3348, 2954, 2928, 2857, 1466, 1252, 1097, 837, 775. ^{1}H-NMR (300 MHz,

$CDCl_3$): 3.32–3.50 (*m*, 4 H); 1.60–1.77 (*m*, 2 H); 1.36–1.50 (*m*, 2 H); 0.93 (*d*, *J* = 6.7, 3 H); 0.90 (*d*, *J* = 6.7, 3 H); 0.89 (*s*, 9 H); 0.03 (*s*, 6 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 68.2; 67.9; 37.2; 33.1; 25.8; 18.2; 17.7; 17.6; −5.4.

*Ethyl (2*E*,4*S*,6*R*)-7-{[(*tert*-Butyl)(dimethyl)silyl]oxy}-4,6-dimethylhept-2-enoate* (**9**). To a stirred soln. of DMSO (1.4 ml, 20.32 mmol) in CH_2Cl_2 (30 ml) was added oxalyl chloride (1.1 ml, 12.7 mmol) at −78°, and the resulting soln. was stirred for 15 min. A soln. of **8** (2.5 g, 10.16 mmol) in CH_2Cl_2 (10 ml) was added dropwise at −78° over 30 min. After stirring the mixture for an additional 30 min, Et_3N (4.20 ml, 30.48 mmol) was added, and the mixture was stirred for 0.5 h at −78° and then for 0.5 h at 0°. The reaction was then quenched with sat. aq. NH_4Cl soln. (20 ml), and then the mixture was extracted with CH_2Cl_2 (2 × 30 ml). The combined org. layers were washed with H_2O (30 ml), brine (20 ml), dried (Na_2SO_4), and concentrated *in vacuo*. To a stirred soln. of crude aldehyde in benzene was added the stabilized ylide Ph_3PCHCO_2Et (5.60 g, 15.2 mmol), and the mixture was refluxed for 12 h and then concentrated *in vacuo*. Solvent was removed under reduced pressure, followed by purification of the residue by CC (AcOEt/hexane 5:95) to give **9**. Colorless liquid. $[\alpha]_D^{25} = +17.9$ (*c* = 1.0, $CHCl_3$). IR (KBr): 2957, 2859, 1722, 1652, 1465, 1367, 1259, 1180, 1094, 1042, 840, 775. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.76 (*dd*, *J* = 15.8, 8.3, 1 H); 5.75 (*d*, *J* = 15.8, 1 H); 4.17 (*q*, *J* = 14.3, 6.7, 2 H); 3.37 (*dd*, *J* = 5.2, 1.5, 2 H); 2.32–2.51 (*m*, 1 H); 1.44–1.67 (*m*, 2 H); 1.29 (*t*, *J* = 6.7, 3 H); 1.06–1.15 (*m*, 1 H); 1.06 (*d*, *J* = 6.7, 3 H); 0.89 (*s*, 9 H); 0.86 (*d*, *J* = 6.7, 3 H); 0.03 (*s*, 6 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 166.7; 154.3; 119.7; 68.3; 60.0; 39.8; 34.1; 33.3; 25.8; 20.4; 18.2; 16.5; 14.2; −5.4. ESI-MS: 337 ($[M+Na]^+$). HR-ESI-MS: 337.2174 ($[M+Na]^+$, $C_{17}H_{34}NaO_3Si^+$; calc. 337.2175).

*Ethyl (4*R*,6*R*)-7-{[(*tert*-Butyl)(dimethyl)silyl]oxy}-4,6-dimethylheptanoate* (**10**). To a stirred soln. of **9** (2.0 g, 6.36 mmol) in AcOEt (10 ml), under N_2 was added Pd/C (10%; 35 mg). The mixture was flushed with N_2 and then stirred under H_2 for *ca.* 2 h until complete consumption of the starting material. The resulting mixture was diluted with Et_2O (20 ml) and then filtered through a pad of *Celite* and concentrated *in vacuo*. The crude product was purified by CC (5% AcOEt/hexane) to give **10** (1.93 g, 96% yield). Colorless oil. $[\alpha]_D^{25} = +3.8$ (*c* = 1.2, $CHCl_3$). IR (KBr): 2956, 1738, 1636, 1253, 1094, 772, 570. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.10 (*q*, *J* = 14.3, 6.7, 2 H); 3.41 (*dd*, *J* = 9.8, 6.0, 1 H); 3.33 (*dd*, *J* = 9.8, 6.0, 1 H); 2.18–2.34 (*m*, 2 H); 1.28–1.75 (*m*, 6 H); 1.26 (*t*, *J* = 6.7, 3 H); 0.90 (*d*, *J* = 6.0, 3 H); 0.89 (*s*, 9 H); 0.87 (*d*, *J* = 6.0, 3 H); 0.02 (*s*, 6 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 174.0; 68.2; 60.1; 40.7; 33.0; 31.8; 31.5; 29.6; 25.9; 20.0; 18.2; 17.3; 14.2; −5.4. ESI-MS: 339 ($[M+Na]^+$). HR-ESI-MS: 339.2321 ($[M+Na]^+$, $C_{17}H_{36}NaO_3Si^+$; calc. 339.2331).

*(4*R*,6*R*)-7-{[(*tert*-Butyl)(dimethyl)silyl]oxy}-4,6-dimethylheptanoic acid* (**11**). $LiOH \cdot H_2O$ (0.79 g, 18.9 mmol) was added in portions to a cooled soln. (0°) of **10** (2.0 g, 6.32 mmol) in 30 ml of MeOH/H_2O (3:1), and stirring was continued for 2 h at r.t. The mixture was then concentrated *in vacuo*, and the residue was diluted with AcOEt (30 ml), washed with sat. aq. NH_4Cl and extracted with AcOEt (3 × 20 ml). The combined org. layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Removal of solvent, followed by CC (20% AcOEt/hexane) afforded **11** (1.70 g, 93% yield). Colorless liquid. $[\alpha]_D^{25} = +5.0$ (*c* = 0.7, $CHCl_3$). IR (KBr): 2956, 2930, 2858, 1711, 1464, 1414, 1253, 1094, 938, 839, 775, 667. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.30–3.45 (*m*, 2 H); 2.24–2.42 (*m*, 2 H); 1.06–1.78 (*m*, 6 H); 0.92 (*d*, *J* = 6.7, 3 H); 0.89 (*s*, 9 H); 0.88 (*d*, *J* = 6.7, 3 H); 0.03 (*s*, 6 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 180.2; 68.1; 40.6; 33.0; 31.5; 31.2; 29.6; 25.9; 19.9; 18.3; 17.4; −5.3 . ESI-MS: 311 ($[M+Na]^+$). HR-ESI-MS: 311.2028 ($C_{15}H_{32}NaO_3Si^+$, $[M+Na]^+$; calc. 311.2018).

*(4*S*)-4-Benzyl-3-[(4*R*,6*R*)-7-{[(*tert*-butyl)(dimethyl)silyl]oxy}-4,6-dimethylheptanoyl]-1,3-oxazolidin-2-one* (**12**). To a stirred soln. of **11** (3.0 g, 10.41 mmol) in THF (35 ml) at −20° was added Et_3N (3.50 ml, 26.04 mmol), followed by PivCl (1.3 ml, 10.41 mmol). After stirring for 1 h at −20°, LiCl (0.66 g, 15.62 mmol), and then by (*S*)-1,3-oxazolidin-2-one (2.0 g, 11.45 mmol) were added at the same temp. The stirring was continued for 1 h at −20° and then 2 h at 0°. The reaction was then quenched with sat. NH_4Cl soln. (20 ml), and the mixture was extracted with AcOEt (2 × 30 ml). The combined org. layers were washed with brine (30 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by CC (AcOEt/hexane 1:16) to give **12** (4.33 g, 93%). Viscous liquid. $[\alpha]_D^{25} = +38.8$ (*c* = 1.0, $CHCl_3$). IR (KBr): 2954, 2928, 2857, 1784, 1700, 1461, 1386, 1353, 1251, 1208, 1093, 839, 772, 701, 591. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.15–7.38 (*m*, 5 H); 4.54–4.67 (*m*, 1 H); 4.09–4.23 (*m*, 2 H); 3.43 (*dd*, *J* = 9.8, 5.2, 1 H); 3.25–3.40 (*m*, 2 H); 2.78–3.03 (*m*, 2 H); 2.69 (*dd*, *J* = 13.5, 9.8, 1 H); 1.08–

1.80 (*m*, 6 H); 0.95 (*d*, *J* = 6.0, 3 H); 0.89 (*s*, 9 H); 0.88 (*d*, *J* = 6.7, 3 H); 0.03 (*s*, 6 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 173.6; 153.3; 135.3; 129.3; 128.8; 127.2; 68.2; 66.0; 55.1; 40.8; 37.8; 33.1; 33.0; 30.8; 29.7; 25.9; 20.0; 18.3; 17.4; −5.3. ESI-MS: 470 ($[M+Na]^+$). HR-ESI-MS: 470.2714 ($[M+Na]^+$, $C_{25}H_{41}NNaO_4Si^+$; calc. 470.2703).

*(4*S*)-4-Benzyl-3-[(2*S*,4*S*,6*R*)-7-{[(*tert*-butyl)(dimethyl)silyl]oxy}-2,4,6-trimethylheptanoyl]-1,3-oxazolidin-2-one* (**13**). To a stirred soln. of **12** (2.0 g, 4.47 mmol) in dry THF (20 ml) at −78°, LDA (1M soln. in THF, 6.75 ml, 6.75 mmol) was added slowly dropwise with stirring under N_2. After stirring at −78° for 30 min, MeI (0.83 ml, 13.42 mmol) was added dropwise and then stirring was continued for another 2 h at −78°. Then, the reaction was quenched with sat. NH_4Cl (10 ml), and the mixture was warmed to r.t. and then extracted with AcOEt (2 × 30 ml). The combined org. extracts were washed with brine (30 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by CC (AcOEt/hexane 1:19) to afford **13** (1.87 g, 91%). Colorless liquid. $[\alpha]_D^{25} = +41.6$ (*c* = 1.3, $CHCl_3$). IR (KBr): 2956, 2928, 2857, 1783, 1699, 1460, 1385, 1351, 1249, 1208, 1096, 839, 774, 700. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.17–7.37 (*m*, 5 H); 4.55–4.68 (*m*, 1 H); 4.08–4.22 (*m*, 2 H); 3.77–3.93 (*m*, 1 H); 3.22–3.47 (*m*, 3 H); 2.70 (*dd*, *J* = 12.8, 9.8, 1 H); 1.25–1.98 (*m*, 5 H); 1.20 (*d*, *J* = 6.7, 3 H); 0.96–1.12 (*m*, 1 H); 0.89 (*s*, 9 H); 0.88 (*d*, *J* = 6.7, 6 H); 0.03 (*s*, 6 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 177.2; 152.9; 135.2; 129.4; 128.8; 127.2; 68.3; 65.9; 55.2; 41.2; 40.4; 37.8; 35.2; 33.0; 28.1; 25.9; 20.7; 18.5; 18.3; 17.4; −5.3. ESI-MS: 484 ($[M+Na]^+$). HR-ESI-MS: 484.2875 ($[M+Na]^+$, $C_{26}H_{43}NaO_4Si^+$; calc. 484.2859).

*(2*S*,4*R*,6*R*)-7-{[(*tert*-Butyl)(dimethyl)silyl]oxy}-2,4,6-trimethylheptan-1-ol* (**5**). To a stirred soln. of **13** (1.80 g, 3.90 mmol) in THF (20 ml) at 0° was added $LiBH_4$ (258 mg, 11.72 mmol) portionwise. The mixture was stirred for 2 h at the same temp., and then, the reaction was quenched with sat. aq. NH_4Cl, and the mixture was extracted with AcOEt (3 × 20 ml). The combined org. layers were dried (Na_2SO_4) and concentrated under reduced pressure, and the crude product was purified by CC (10%, AcOEt/hexane) to afford **5** (1.03 g, 92%). Viscous liquid. $[\alpha]_D^{25} = -5.8$ (*c* = 1.0, $CHCl_3$). IR (KBr): 3351, 2956, 2928, 2858, 1465, 1383, 1253, 1098, 1040, 838, 775, 667. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.29–3.55 (*m*, 4 H); 2.60 (*s*, 1 H); 0.96–1.88 (*m*, 7 H); 0.93 (*d*, *J* = 7.5, 3 H); 0.90 (*d*, *J* = 6.7, 3 H); 0.89 (*s*, 9 H); 0.88 (*d*, *J* = 6.7, 3 H); 0.03 (*s*, 6 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 68.1; 67.9; 41.2; 41.0; 33.0; 27.6; 25.9; 21.0; 18.3; 17.9; 17.5; −5.3. ESI-MS: 289 ($[M+H]^+$). HR-ESI-MS: 311.2398 ($[M+Na]^+$, $C_{16}H_{36}NaO_2Si^+$; calc. 311.2382).

*(2*R*,4*S*,6*S*)-7-(Benzyloxy)-2,4,6-trimethylheptan-1-ol* (**14**). To a stirred soln. of NaH (0.55g (50% with mineral oil), 11.46 mmol) in dry THF (10 ml) was added **5** (3.0 g, 10.42 mmol) in dry THF (20 ml) at 0°. The mixture was stirred for 20 min, and then a soln. of BnBr (1.3 ml, 10.42 mmol) in excess anh. THF was added slowly dropwise. The resulting mixture was allowed to be stirred at r.t. for 2 h. Upon completion, the reaction was quenched with H_2O, and the mixture was extracted with AcOEt (3 × 20 ml). The org. extracts were washed with brine and dried (Na_2SO_4). Evaporation of the solvent, followed by purification of the crude product by flash chromatography (FC; 4% AcOEt/ hexane) afforded the benzyl ether (3.62 g, 92%) as a colorless liquid.

The crude product was dissolved in dry THF (20 ml) at 0°, and then 9.6 ml of Bu_4NF (1M in THF) was added. The resulting mixture was stirred at r.t. for 6 h. After completion, the reaction was quenched with sat. NH_4Cl soln. (10 ml), and the mixture was extracted with AcOEt (2 × 30 ml). The combined org. layers were washed with brine (30 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by CC (AcOEt/hexane 1:9) to give **5** (2.3 g, 90%). Viscous liquid. $[\alpha]_D^{25} = +7.5$ (*c* = 2.5, $CHCl_3$). IR (KBr): 3418, 2956, 2919, 2869, 1457, 1370, 1101, 1034, 740. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.34–7.19 (*m*, 5 H); 4.50–4.42 (*m*, 2 H); 3.46 (*dd*, *J* = 4.9, 9.8, 1 H); 3.36–3.27 (*m*, 2 H); 3.23–3.18 (*m*, 2 H); 1.87–1.80 (*m*, 1 H); 1.61–1.55 (*m*, 1 H); 1.40–1.26 (*m*, 2 H); 0.97–0.84 (*m*, 12 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 138.6; 128.2; 127.4; 127.3; 75.7; 72.93; 68.0; 41.5; 41.0; 32.9; 30.8; 27.6; 20.9; 18.2; 17.5. ESI-MS: 282 ($[M+NH_4]^+$).

*Benzyl (2*S*,4*S*,6*S*)-2,4,6-Trimethylnonyl Ether* (**15**). To a stirred soln. of **14** (2.0 g, 7.6 mmol) in dry CH_2Cl_2(20 ml) were added Et_3N (1.3 ml, 9.1 mmol), TsCl (1.50g, 7.6 mmol), and a cat. amount of DMAP (46 mg, 0.37 mmol). The resulting mixture was stirred for 3 h. After complete conversion (TLC), the reaction was quenched with NH_4Cl soln., and the mixture was extracted with AcOEt (3 × 20 ml). Removal of the solvent, followed by purification on CC (5% AcOEt/hexane), gave the pure tosyl derivative. To a round-bottom flask equipped with an activated Mg turnings (0.59 g, 24.0 mmol,

3.4 equiv.), EtBr (1.86 ml, 25.2 mmol, 3.5 equiv.) in Et_2O (20 ml) was added slowly. After complete addition, the mixture was heated to reflux (*ca.* 30 min) until initiation of the reaction. The mixture was cooled to $-20°$, and then tosylate (3.0 g, 7.18 mmol) was added slowly. To this mixture, a soln. of Li_2CuCl_4 (0.1M in THF, 7 ml, 0.718 mmol, 0.1 equiv.) was slowly added at $-20°$. The resulting mixture was stirred vigorously overnight at r.t., and the reaction was quenched with sat. aq. NH_4Cl (20 ml) at 0°, and the mixture was extracted with Et_2O (3×20 ml). Removal of the solvent, followed by CC gave **15** (82%). Colorless liquid. $[\alpha]_D^{25} = +2.0$. ($c = 1.0$, $CHCl_3$). IR (KBr): 3449, 2955, 2919, 2857, 1637, 1457, 1371, 1101, 760. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.35–7.21 (*m*, 5 H); 4.51–4.42 (*m*, 2 H); 3.30 (*dd*, $J = 5.2$, 1 H); 3.18 (*dd*, $J = 6.7$, 1 H); 1.90–1.78 (*m*, 1 H); 1.65–1.44 (*m*, 2 H); 1.44–1.15 (*m*, 6 H); 1.03–0.79 (*m*, 14 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 138.8; 128.2; 127.4; 127.3; 75.9; 73.0; 45.2; 41.8; 38.9; 30.9; 29.7; 27.6; 20.9; 20.4; 20.0; 18.4; 14.5. ESI-MS: 294 ($[M + NH_4]^+$).

(2S,4S,6S)-2,4,6-Trimethylnonan-1-ol (**16**). To a stirred soln. of **15** (1.6 g, 5.8 mmol) in AcOEt (10 ml) under N_2 was added Pd/C (10%, 35 mg). The soln. was flushed with N_2 and then stirred under H_2 for *ca.* 2 h until complete consumption of the starting material. The resulting mixture was diluted with Et_2O (60 ml), filtered through a pad of *Celite*, and concentrated *in vacuo*. The crude product was purified by CC (AcOEt/hexane 1:9) to yield **16** (1.1g, 95% yield). Colorless oil. $[\alpha]_D^{25} = -7.7$ ($c = 2.1$, $CHCl_3$). IR (KBr): 3450, 2924, 2855, 1633, 1376, 1215, 1085, 759. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.54–3.32 (*m*, 2 H); 2.06–1.96 (*m*, 1 H); 1.77–1.42 (*m*, 3 H); 1.37–1.11 (*m*, 6 H); 0.95–0.79 (*m*, 14 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 68.2; 45.1; 41.2; 38.7; 33.0; 29.7; 27.4; 20.8; 20.4; 19.9; 17.5; 14.4.

Ethyl (2E,4S,6S,8S)-2,4,6,8-Tetramethylundec-2-enoate (**4**). To a stirred soln. of 2-iodobenzoic acid (IBX; 2.48 g, 8.85 mmol) in DMSO (6 ml) at 25°, was added slowly dropwise a soln. of **16** (1.1 g, 5.9 mmol) in CH_2Cl_2 (15 ml). The resulting mixture was stirred at 25° for 3 h. The solid was filtered and washed with Et_2O. The filtrate was washed with sat. aq. $NaHCO_3$ soln., H_2O, and brine, and then dried (Na_2SO_4). The solvent was removed under reduced pressure to furnish the crude aldehyde. To this aldehyde in CH_2Cl_2 (20 ml) was added ethyl 2-(triphenylphosphoranylidene)propanoate (3.30 g, 9.46 mmol), and the resulting mixture was stirred for 12 h at r.t. The solvent was concentrated under reduced pressure and purified by CC (3% AcOEt/hexane) to afford **4** (1.3 g, 86%). Colorless liquid. $[\alpha]_D^{25} = +17.9$ ($c = 1.0$, $CHCl_3$). IR (KBr): 3449, 2958, 2924, 2871, 1713, 1648, 1457, 1268, 1101, 1035, 751. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.44 (*d*, $J = 10.1$, 1 H); 4.20 (*q*, $J = 7.1$, 2 H); 2.66–2.53 (*m*, 1 H); 1.84 (*s*, 3 H); 1.46–1.14 (*m*, 10 H); 1.12–0.77 (*m*, 15 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 168.3; 148.0; 126.1; 60.2; 45.5; 44.3; 39.2; 30.8; 29.6; 28.1; 20.5; 20.4; 19.9; 14.3; 14.2; 12.3. ESI-MS: 291 ($[M + Na]^+$). HR-ESI-MS: 291.2322 ($[M + Na]^+$, $C_{17}H_{32}NaO_2^+$; calc. 291.2300).

(2E,4S,6S,8S)-2,4,6,8-Tetramethylundec-2-enal (**1**) [8]. To a cooled ($-78°$) soln. of **4** (250 mg, 0.93 mmol) in dry CH_2Cl_2 (3 ml), DIBAL-H (1.0 ml, 1.0 mmol, 20% soln. in toluene) was added slowly over 5 min. The resulting mixture was stirred for 30 min at $-78°$, before quenching the reaction with sodium potassium tartarate soln. (5 ml). The mixture was then stirred at r.t. until it became clear soln. The aq. layer was extracted with CH_2Cl_2 (3×10 ml), and the combined org. layers were concentrated *in vacuo*. Purification of the residue (FC; AcOEt/hexane 2:98) gave *siphonarienal* (**1**; 80%). Colorless liquid. $[\alpha]_D^{25} = +15.8$ ($c = 1.0$, $CHCl_3$). IR (KBr): 3447, 2959, 2924, 2871, 2706, 1690, 1644, 1459, 1378, 1014, 809. ^{1}H-NMR (300 MHz, $CDCl_3$): 9.39 (*s*, 1 H); 6.22 (*d*, $J = 9.8$, 1 H); 2.91–2.76 (*m*, 1 H); 1.77 (*s*, 3 H); 1.53–1.25 (*m*, 4 H); 1.24–1.10 (*m*, 3 H); 1.04 (*d*, $J = 6.7$, 3 H); 0.95–0.78 (*m*, 12 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 195.4; 160.6; 137.93; 45.5; 44.2; 39.2; 31.2; 29.6; 28.2; 20.4; 20.3; 20.0; 19.9; 14.3; 9.3.

(4E,6S,8S,10S)-4,6,8,10-Tetramethyltridec-4-en-3-one (**2**) [20]. To a stirred soln. of **1** (150 mg, 0.66 mmol) in dry THF was added EtMgBr (0.4 ml of 2M soln.), at $-78°$, and the mixture was stirred for 2 h. The reaction was then quenched with sat. NH_4Cl, and the mixture was extracted with AcOEt ($3 \times$ 5 ml). The combined org. extracts were washed sequentially with H_2O and brine, dried (Na_2SO_4), and filtered. Evaporation of the solvent under reduced pressure afforded the diastereoisomer mixture of allylic alcohol (1:1), which was then dissolved in dry CH_2Cl_2 (6 ml) and treated with *Dess–Martin* periodinane (450 mg) at 0° for 30 min. The mixture was filtered through a pad of *Celite*, washed with CH_2Cl_2, and the reaction was quenched with sat. aq. $NaHCO_3$ soln. The aq. layer was then extracted with CH_2Cl_2 (3×5 ml), and washed with H_2O and then brine. The org. extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to furnish the crude product which was then purified by CC (AcOEt/hexane

2:98) to yield **2** (90%). $[\alpha]_D^{25} = +25.2$ ($c = 1.0$, $CHCl_3$). IR (KBr): 3451, 2958, 2925, 2871, 1672, 1639, 1458, 1376, 1256, 1047, 799. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.34 (*d*, *J* = 9.2, 1 H); 2.75–2.64 (*m*, 3 H); 1.80 (*s*, 3 H); 1.54–1.15 (*m*, 10 H); 1.10 (*t*, *J* = 7.3, 3 H); 1.05 (*d*, *J* = 6.6, 3 H); 0.87 (*t*, *J* = 7.3, 3 H); 0.83 (*d*, *J* = 6.6, 3 H); 0.81 (*d*, *J* = 6.6, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 202.8; 148.2; 135.3; 45.5; 44.4; 39.2; 31.2; 30.3; 29.6; 28.2; 20.6; 20.4; 19.9; 19.9; 14.3; 11.5; 8.9. ESI-MS: 253 ($[M+H]^+$).

*(2*E*,4*S*,6*S*,8*S*)-*N*-Methoxy-*N*,2,4,6,8-pentamethylundec-2-enamide* (**17**). To a stirred soln. of **4** (300 mg, 1.34 mmol) and Me(MeO)NH · HCl (4.0 g, 4.0 mmol) in anh. THF (10 ml) was added ^{i}PrMgCl (2.68 ml, 5.36 mmol, 2M soln. in THF) at $-20°$, and the mixture was stirred for 1 h. Upon completion, the reaction was quenched with sat. aq. NH_4Cl (5 ml), and the mixture was washed with AcOEt (2 × 5 ml). The combined org. layers were dried (Na_2SO_4), concentrated *in vacuo*, and purified by CC (AcOEt/hexanes 5:95) to give **17** (280 mg, 75%). Liquid. $[\alpha]_D = +11.1$ ($c = 1.0$, $CHCl_3$). IR (KBr): 3448, 2923, 2855, 1624, 1456, 1219, 769, 668. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.44 (*d*, *J* = 10.3, 1 H); 3.38 (*s*, 3 H); 2.69–2.54 (*m*, 1 H); 1.88 (*s*, 3 H); 1.55–0.93 (*m*, 14 H); 0.99 (*d*, *J* = 6.7, 3 H); 0.88 (*t*, *J* = 6.7, 2 H); 0.86 (*d*, *J* = 6.7, 3 H); 0.82 (*d*, *J* = 6.7, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 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. ESI-MS: 284 ($[M+H]^+$).

*4-Hydroxy-3,5-dimethyl-6-[(2*E*,4*S*,6*S*,8*S*)-4,6,8-trimethylundec-2-en-2-yl]-2*H*-pyran-2-one* (**3**) [22]. To a freshly prepared 1.0M soln. of LDA (1.20 ml) in anh. THF at $-20°$ was added a soln. of **17** (150 mg, 0.53 mmol) in anh. THF (5 ml) dropwise, and the mixture was stirred for 30 min at 0°. To this mixture, a soln. of **18** (252 mg, 1.59 mmol) in anh. THF (5 ml) was added dropwise at 0°, the resulting mixture was stirred for another 30 min at the same temp. After completion, the reaction was quenched with sat. aq. NH_4Cl (6 ml) at 0°, and the mixture was allowed to warm to r.t. The aq. layer was separated and washed with AcOEt (2 × 5 ml). The combined org. layers were dried (Na_2SO_4) and concentrated *in vacuo* to afford crude **19** (415 mg) as a liquid. Without further purification, the compound **19** was treated with DBU (1.0 ml, 6.811 mmol) in anh. toluene under reflux for 4 h. The solvent was removed under reduced pressure, then the residue was diluted with CH_2Cl_2 (10 ml) and washed with H_2O (3 ml). The aq. layer was again washed with CH_2Cl_2 (2 × 10 ml). The combined org. layers were dried (Na_2SO_4) , concentrated *in vacuo*, and purified by CC (AcOEt/hexane 1:4) to give **3**. Solid. M.p. 126–128°. $[\alpha]_D = +58$ ($c = 0.2$, $CHCl_3$). IR (KBr): 3201, 2923, 2858, 1655, 1455, 1375, 1226, 755. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.37–5.32 (*m*, 1 H); 2.68–2.58 (*m*, 1 H); 2.03 (*s*, 3 H); 1.97 (*s*, 3 H); 1.86 (*s*, 3 H); 1.52–1.42 (*m*, 2 H); 1.40–1.01 (*m*, 8 H); 0.91 (*t*, *J* = 6.4, 3 H); 0.86 (*d*, *J* = 6.0, 3 H); 0.85 (*d*, *J* = 6.0, 3 H); 0.80 (*d*, *J* = 6.4, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 165.2; 164.5; 159.6; 146.9; 126.2; 105.4; 98.7; 45.9; 44.8; 39.4; 30.6; 29.5; 28.3; 21.4; 20.2; 20.1; 20.0; 14.8; 14.4; 11.5; 8.5. ESI-MS: 352 ($[M+NH_4]^+$).

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