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Practical synthesis of 1,5-dimethyl substituted conjugated polyenes from geranyl acetate

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ABSTRACT

A protocol to synthesize 1,5-dimethyl substituted conjugated polyenes via dehydrogenation of geranyl acetate was established. C_5 unit elongation to multi-1,5-dimethyl substituted conjugated polyenes was also achieved via Horner–Wadsworth–Emmons olefination in good yields and good selectivities.

1. Introduction

There is a large and diverse group of natural products containing the 1,5-dimethyl substituted conjugated polyene unit. Some of these natural products include malabaricanes,[1] isomalabaricanes,[2] lycopenes,[3] calbistrins,[4] retinoids and carotenoids[5] that possess interesting biological activities (Fig. 1). In the course of making some of these natural products, we are interested to develop a practical synthesis for the preparation of multi-1,5-dimethyl substituted type conjugated polyenes.

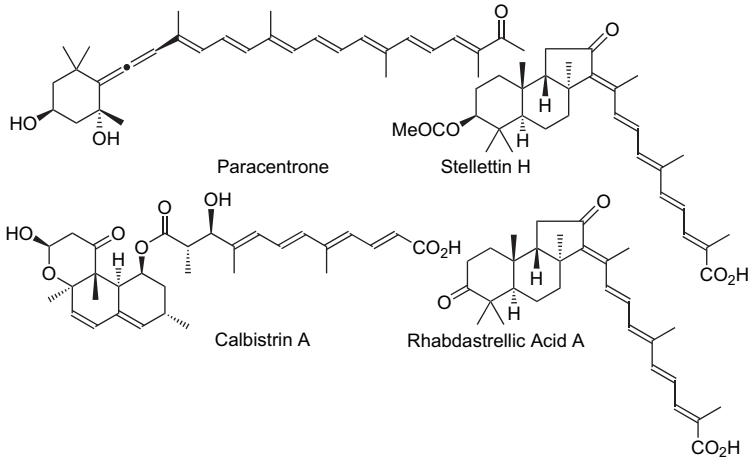

Figure 1.

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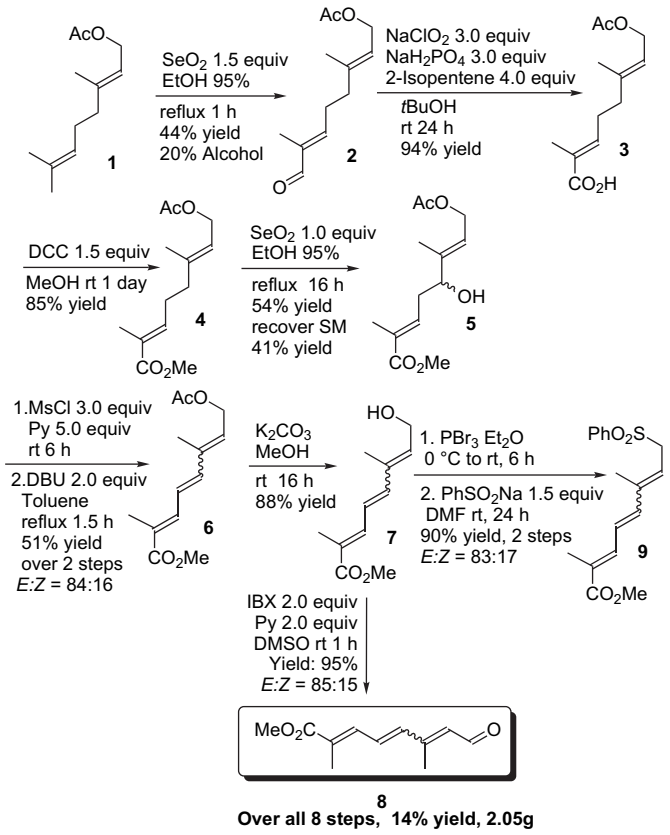
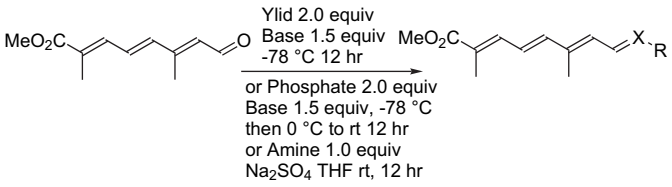


Scheme 1.

Table 1
Coupling reactions of 8-methoxy-8-oxo-dehydrogeranal



Entry	Reagent	Yield[a] (%)	Ratio[b]
1[c]	Ph_3P CO_2Me	80	85:15
2[c]	$ClPh_3P$ Ph	95	76:24[e]
3[c]	Et—PPh_3Br	52	55:45
4[c]	$BrPh_3P$ Ph	91	83:17
5[d]	$(EtO)_2OP$ CO_2Me	90	88:12
6[e]	Ph—NH_2	88[f]	79:21
7[e]	OH, H_2N (S), (R) Ph	95[f]	86:14

[a] Isolated yield unless otherwise stated.
[b] Ratio was determined by ^1H NMR and/or ^{13}C NMR.
[c] Wittig reaction with corresponding ylide.
[d] HWE olefination with corresponding phosphate.
[e] Schiff base formation.
[f] Crude yield.

Nature uses isopentenyl pyrophosphate (IPP) or dimethylallyl pyrophosphate (DMAP) as building blocks for the synthesis of conjugated polyene chain. Enzymes assemble these basic C_5 units providing a diverse range of isoprenoids.[6] The most common strategies employed by chemists to access 1,5-dimethyl substituted conjugated polyenes involve the use of the Wittig reaction, Horner–Wadsworth–Emmons (HWE) reaction, Julia olefination and transition metal catalyzed cross-coupling reactions.[7] Recently, Koo et al. reported an efficient synthesis of a carotenoidal conjugated polyene chain structure using 4-bromo-3-methyl-2-butenyl phenyl sulfide as a chain-extension C_5 unit.[8] However, protocols using natural occurring unsaturated polyene backbone for the construction of conjugated polyene skeletons are still rare. Herein, we present the synthesis of multi-1,5-dimethyl substituted conjugated polyenes using dehydrogenated geranyl acetate **6** (Scheme 1).

2. Results and discussion

Dehydrogenated geranyl acetate **6** was synthesized in five steps from naturally occurring geranyl acetate **1** as shown in Scheme 1. In our synthetic route, allylic oxidations using SeO_2 were employed twice.[9] Aldehyde **2** was obtained as major product in 44 % yield together with the corresponding alcohol in 20% yield. This alcohol can be easily recycled to the desired aldehyde **2**. On the other hand, alcohol[9b] **5** was obtained as major product in 54% yield (starting material recovered in 41% yield). Efforts to increase the yield by prolonging reaction time and loading excess of SeO_2 resulted in the increase in over-oxidized ketone side product. Acetate **6** was then converted to aldehyde **8** in another two steps. Overall, aldehyde **8** was obtained in 14% yield over eight steps (2.05 g, isomer ratio=85:15).

The aldehyde **8** (8-methoxy-8-oxo-dehydrogeranal) is a versatile intermediate, which can be readily converted to different conjugated polyene compounds (Table 1) or elongated to multi-1,5-dimethyl substituted conjugated polyenes (Scheme 3). Before we proceeded to C_5 chain elongation, a model study was carried out. To our delight, olefination reaction proceeded smoothly with good yields and good selectivities using acceptor synthon **8**. These results are shown in Table 1. From the single crystal X-ray structure of **A**[10] (Table 1, entry 1), we were able to further trace back and confirm the stereochemistry of the major isomer of **8**. It was found that all double bonds adopted the *E* conformation (Fig. 2).

With this information in hand, we further proceeded to investigate C_5 unit elongation of **8** to construct multi-1,5-dimethyl substituted conjugated polyenes. Prenyl acetate is a naturally abundant hemiterpene and has been used as C_5 elongation unit synthon by Rein and Akermark.[11] However, phosphate **14** they obtained was a mixture of isomers (*E*/*Z*=55:45), which resulted in moderate selectivity of the corresponding HWE olefination.[11] We solved the problem by using SeO_2 promoted selective allylic oxidation of prenyl acetate, under which conditions *E*-alcohol **11**

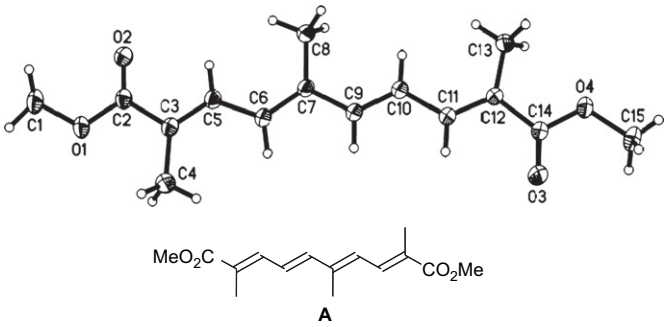
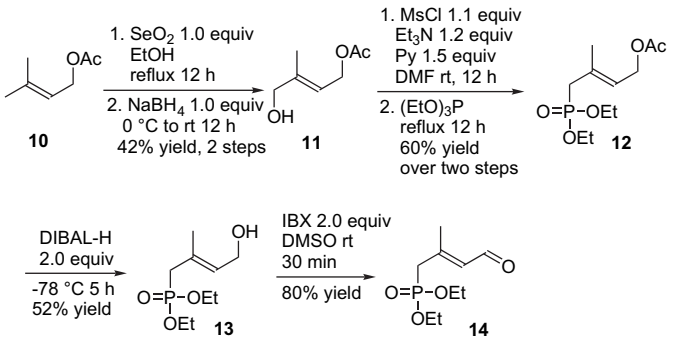


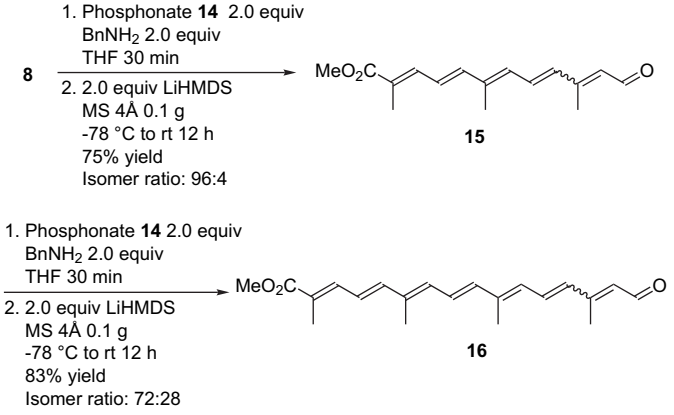
Figure 2.



Scheme 2.

was obtained almost exclusively. Over another three steps of reaction (Scheme 2), we were able to synthesize phosphonate **14** in an excellent isomer ratio (*E*/*Z*=96:4).

With the C_5 unit **14** synthon in hand, we successfully elongated aldehyde **8** using Horner–Wadsworth–Emmons olefination to form 12-methoxy-12-oxo-dehydrofarnesal (**15**) (Scheme 3). After that, we further elongated aldehyde **15** to form 16-methoxy-16-oxo-dehydrogeranylgeranal (**16**). Both elongations proceeded with good yields and good selectivities. It is worth noting that the corresponding imines were obtained after the reaction. The imines were converted to the desired aldehyde during silica gel flash chromatography purification.



Scheme 3.

3. Conclusion

In conclusion, we have developed a new protocol to carry out large-scale preparation of 1,5-dimethyl substituted conjugated polyene via dehydrogenation of geranyl acetate. In addition, elongation of 8-methoxy-8-oxo-dehydrogeranal to multi-1,5-dimethyl substituted conjugated polyenes using Horner–Wadsworth–Emmons olefination was also achieved in good yields and good selectivities. Efforts to utilize them for the synthesis of natural products are in progress.

4. Experimental section

4.1. General

All reagents were of the highest purity available, obtained from commercial suppliers and used as received. Solvents were of analytical grade. Analytical thin layer chromatography (TLC) was performed using Merck 60 F_{254} precoated silica gel plate (0.2 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with basic solution of potassium permanganate or acidic solution of ceric molybdate, followed by heating on a hot plate. Flash chromatography was performed using Merck silica gel 60 with distilled solvents. Columns were typically packed as slurry and equilibrated with hexane prior to use. Infrared spectra were recorded on a Shimadzu IR Prestige-21 FT-IR Spectrometer. Liquid samples were examined as film between NaCl or KBr salt plates. Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectroscopy were performed on a Bruker Advance 300, 400 and 500 NMR spectrometers. Low resolution mass spectrum analysis was performed on Finnigan polaris Q, GC–MS XP mass spectrometer (Thermo Electron Corporation). High resolution mass spectral analysis (HRMS) was performed on Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). X-ray crystallography analysis was performed on Bruker X8 APEX X-ray diffractometer.

4.2. Synthesis of 8-methoxy-8-oxo-dehydrogeranal (8)

*4.2.1. (2E,6E)-8-Acetoxy-2,6-dimethylocta-2,6-dienoic aldehyde (**2**)*

To a round-bottom flask equipped with a magnetic stirring bar were added geranyl acetate **1** (9.75 g, 50 mmol, 1.0 equiv), SeO_2 (11.91 g, 100 mmol, 2.0 equiv) and EtOH (95%, 250 mL). The mixture was heated at reflux for 2 h. The mixture was diluted with ethyl acetate (200 mL). The aqueous layer was extracted with ethyl acetate (3×50 mL) and the combined organic layers were washed with brine (3×100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residual crude product was purified by flash column chromatography to afford desired aldehyde **3** in 44% yield as a colourless oil. The corresponding alcohol was also isolated in 20% yield. All spectra data of aldehyde **2** match the previous reported results.[12]

*4.2.2. (2E,6E)-8-Acetoxy-2,6-dimethylocta-2,6-dienoic acid (**3**)*

To an oven-dried round-bottom flask equipped with a magnetic stirring bar were added aldehyde **2** (5.45 g, 26 mmol, 1.0 equiv), 2-methyl-2-butene (200 mL) and ^{t}BuOH (200 mL). The mixture was cooled to 0 °C and a mixture of NaH_2PO_4 (42 g, 350 mmol, 13 equiv) and $NaClO_2$ (70% technical grade, 42 g, 33 mmol, 13 equiv) aqueous solution was added via pressure-equilibrating dropping funnel at 0 °C. The reaction mixture was gradually warmed up to room temperature and was stirred for another 12 h. The mixture was diluted with ethyl acetate (200 mL). The aqueous layer was extracted with ethyl acetate (3×50 mL) and the combined organic layers were washed with water (50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residual crude product was purified by flash column chromatography to afford acid **3** in 94% yield as a colourless oil. R_f: 0.25 (hexane/ethyl acetate=4:1). ^{1}H NMR (400 MHz, $CDCl_3$): 10.0–9.0 (br, 1H, CO_2H), 6.83 (t, *J*=7.2 Hz, 1H, C=C*H*), 5.34 (t, *J*=6.9 Hz, 1H, C=C*H*), 4.58 (d, *J*=7.2 Hz, 2H, CH_2OAc), 2.31 (q, *J*=7.4 Hz, 2H, =CH–CH_2), 2.15 (t, *J*=7.4 Hz, 2H, CH_2–C(Me)=CH), 2.02 (s, 3H, C(O)–*Me*), 1.80 (s, 3H, *Me*), 1.69 (s, 3H, *Me*). ^{13}C NMR (100 MHz, $CDCl_3$): 173.3, 171.2, 143.9, 140.9, 127.5, 119.2, 61.2, 37.8, 27.0, 21.0, 16.4, 12.0. HRMS (CI): *m*/*z* calculated for $C_{12}H_{17}O_4$ $[M-H]^+$: 225.1127, found $[M-H]^+$: 225.1123. FTIR (KBr): ν 3439 (br), 2980, 1720 (br), 1640 cm^{-1}.

*4.2.3. (2E,6E)-Methyl 8-acetoxy-2,6-dimethylocta-2,6-dienoate (**4**)*

To an oven-dried round-bottom flask equipped with a magnetic stirring bar were added acid **3** (10.69 g, 47.2 mmol, 1.0 equiv) and DMAP (610 mg, 5.0 mmol, 0.1 equiv). The mixture was azeotropically dried with dry THF (2×20 mL). Anhydrous methanol (40 mL)

and THF (100 mL) were added via syringe. The mixture was cooled to 0 °C and DCC (1.0 M solution in CH_2Cl_2, 70 mL, 70 mmol, 1.50 equiv) was added via pressure-equilibrating dropping funnel over 30 min. The reaction mixture was gradually warmed to room temperature and was stirred for another 24 h. The reaction mixture was concentrated in vacuo. The mixture was diluted with hexane (200 mL) and filtered through a pad of Celite®. The Celite® was washed with hexane (2×200 mL). The combined organic layers were concentrated in vacuo. The residual crude product was purified by flash column chromatography to afford ester **4** in 85% yield as a colourless oil. R_f: 0.75 (hexane/ethyl acetate=4:1). ^{1}H NMR (400 MHz, $CDCl_3$): 6.69 (td, J=7.4, 1.5 Hz, 1H, =C*H*), 5.34 (tq, J=7.0, 1.2 Hz, 1H, =C*H*), 4.56 (d, J=6.9 Hz, 2H, CH_2–OAc), 3.71 (s, 3H, O*Me*), 2.29 (q, J=7.4 Hz, 2H, =CH–CH_2), 2.14 (t, J=7.5 Hz, 2H, CH_2–C(Me)=CH), 2.03 (s, 3H, C(O)*Me*), 1.81 (s, 3H, *Me*), 1.70 (s, 3H, *Me*). ^{13}C NMR (100 MHz, $CDCl_3$): 171.1, 168.5, 141.4, 141.0, 127.9, 119.1, 61.2, 51.7, 38.0, 26.8, 21.0, 16.4, 12.4. HRMS (CI): m/z calculated for $C_{13}H_{21}O_4$ $[M+H]^+$: 241.1440, found $[M+H]^+$: 241.1339. FTIR (KBr): ν 1760, 1705 (br), 1651 cm^{-1}.

4.2.4. (2E,6E)-Methyl 8-acetoxy-5-hydroxy-2,6-dimethylocta-2,6-dienoate (**5**)

To a round-bottom flask equipped with a magnetic stirring bar were added ester **4** (9.6 g, 40 mmol, 1.0 equiv), SeO_2 (4.4 g, 40 mmol, 1.0 equiv) and ethanol (200 mL, 95%). The mixture was heated at reflux for 24 h. The mixture was diluted with ethyl acetate (100 mL). The organic layer was washed with brine (3×50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residual crude product was purified by flash column chromatography to afford alcohol **5** in 54% yield as a colourless oil. R_f: 0.55 (hexane/ethyl acetate=4:1). ^{1}H NMR (400 MHz, $CDCl_3$): 6.74 (t, J=7.1 Hz, 1H, =C*H*), 5.62 (t, J=6.6 Hz, 1H, =C*H*), 4.62 (d, J=6.7 Hz, 2H, CH_2OAc), 4.17 (t, J=6.3 Hz, 1H, OC*H*), 3.73 (s, 3H, O*Me*), 2.44 (t, J=7.1 Hz, 2H, =CH–CH_2), 2.06 (s, 3H, C(O)*Me*), 1.85 (s, 3H, *Me*), 1.72 (s, 3H, *Me*). ^{13}C NMR (100 MHz, $CDCl_3$): 171.0, 168.3, 142.3, 137.7, 129.7, 120.2, 75.6, 60.8, 51.8, 34.5, 21.0, 12.7, 12.3. HRMS (CI): m/z calculated for $C_{13}H_{21}O_5$ $[M+H]^+$: 257.1389, found $[M+H]^+$: 257.1390. FTIR (KBr): ν 1760, 1695 (br), 1655 cm^{-1}.

4.2.5. (2E,4E,6E)-Methyl 8-acetoxy-2,6-dimethylocta-2,4,6-trienoate (**6**)

To an oven-dried round-bottom flask equipped with a magnetic stirring bar were added alcohol **5** (6.41 g, 25.0 mmol, 1.0 equiv), pyridine (8.1 mL, 100 mmol, 4.0 equiv) and CH_2Cl_2 (100 mL). The mixture was cooled to 0 °C and $MeSO_2Cl$ (5.8 mL, 75 mmol, 3.0 equiv) was added via syringe. The reaction mixture was gradually warmed to room temperature and was stirred for another 6 h. The mixture was poured into ice water (100 mL). The aqueous layer was extracted with ethyl acetate (3×50 mL) and the combined organic layers were washed with saturated $NaHCO_3$ aqueous solution (100 mL), water (50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residual crude product was purified by flash column chromatography to afford a mixture of corresponding allylic chloride and the desired alkene **5** as a colourless oil. The mixture was dissolved in toluene (100 mL) and DBU (5.6 mL, 50 mmol, 2.0 equiv) was added via syringe. The reaction mixture was heated at reflux for 1.5 h. The mixture was diluted with CH_2Cl_2 (3×100 mL). The organic layer was washed with brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residual crude product was purified by flash column chromatography to afford ester **6** in 51% yield as a colourless oil. Isomer ratio=84:16. R_f: 0.76 (hexane/ethyl acetate=4:1). Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$): 7.24 (d, J=7.9 Hz, 1H, =C*H*), 6.55–6.50 (m, 2H, C*H*=C*H*), 5.75 (t, J=6.9 Hz, 1H, =C*H*–CH_2), 4.74 (d, J=6.9 Hz, 2H, CH_2OAc), 3.76 (s, 3H, O*Me*), 2.07 (s, 3H, C(O)*Me*), 1.99 (s, 3H, *Me*), 1.89 (s, 3H, *Me*). ^{13}C NMR (100 MHz, $CDCl_3$): 170.8, 168.7, 142.6, 138.3, 138.0, 128.5, 127.1, 124.0, 61.06, 51.8, 20.9, 12.8, 12.6. HRMS (CI): m/z calculated for $C_{13}H_{18}O_4$ $[M]^+$: 238.1205, found: 238.1210. FTIR (KBr): ν 1760 (br), 1699, 1616, 1543 cm^{-1}.

4.2.6. (2E,4E,6E)-Methyl 8-hydroxy-2,6-dimethylocta-2,4,6-trienoate (**7**)

To a round-bottom flask equipped with a magnetic stirring bar were added ester **6** (3.02 g, 12.7 mmol, 1.0 equiv) and MeOH (100 mL). The mixture was cooled to 0 °C and K_2CO_3 (7.18 g, 52 mmol, 4.0 equiv) was added. The reaction mixture was gradually warmed up to room temperature and was stirred for another 24 h. The mixture was poured into ice water (100 mL). The aqueous layer was extracted with ethyl acetate (3×50 mL) and the combined organic layers were washed with water (50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residual crude product was purified by flash column chromatography to afford alcohol **7** in 88% yield as a colourless oil. R_f: 0.13 (hexane/ethyl acetate=4:1). Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$): 7.29–7.22 (m, 1H, =C*H*), 6.59–6.43 (m, 2H, C*H*=C*H*), 5.83 (t, J=6.7 Hz, 1H, =C*H*–CH_2), 4.34 (d, J=6.7 Hz, 2H, CH_2–OH), 3.76 (s, 3H, O*Me*), 1.98 (s, 3H, *Me*), 1.86 (s, 3H, *Me*). ^{13}C NMR (100 MHz, $CDCl_3$): 168.9, 143.3, 138.7, 135.8, 134.3, 126.7, 123.4, 59.5, 51.8, 12.80, 12.56. HRMS (CI): m/z calculated for $C_{11}H_{16}O_3$ $[M]^+$: 196.1089, found: 196.1088. FTIR (KBr): ν 3427 (br), 1629 (br), 1508 cm^{-1}.

4.2.7. (2E,4E,6E)-Methyl 2,6-dimethyl-8-oxoocta-2,4,6-trienoate (8-methoxy-8-oxo-dehydrogeranal) (**8**)

To a round-bottom flask equipped with a magnetic stirring bar were added alcohol **7** (2.19 g, 11.1 mmol, 1.0 equiv) and DMSO (50 mL). The mixture was cooled to 0 °C and IBX (6.22 g, 22.2 mmol, 2.0 equiv) was added. The reaction mixture was gradually warmed up to room temperature and was allowed to stir for another 3 h. The mixture was poured into ice water (100 mL). The aqueous layer was extracted with ethyl acetate (3×50 mL) and the combined organic layers were washed with water (50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residual crude product was purified by flash column chromatography to afford aldehyde **8** in 95% yield (2.05 g) as a yellow solid, mp 82–83 °C. Isomer ratio=85:15. R_f: 0.25 (hexane/ethyl acetate=4:1). Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$): 10.16 (d, J=7.9 Hz, 1H, C*H*O), 7.29 (d, J=11.1 Hz, 1H, =C*H*), 7.20 (dd, J=15.2, 11.1 Hz, 1H, =C*H*), 6.63 (d, J=15.2 Hz, 1H, =C*H*), 6.06 (d, J=7.9 Hz, 1H, =C*H*), 3.80 (s, 3H, O*Me*), 2.35 (s, 3H, *Me*), 2.06 (s, 3H, *Me*). ^{13}C NMR (100 MHz, $CDCl_3$): 191.2, 168.3, 153.0, 141.2, 136.8, 131.3, 131.2, 130.2, 52.1, 13.2, 13.0. HRMS (CI): m/z calculated for $C_{11}H_{14}O_3$ $[M]^+$: 194.0943, found: 194.0937. FTIR (KBr): ν 1707, 1654 (br) cm^{-1}.

(2*E*,4*Z*,6*E*)-Methyl 2,6-dimethyl-8-oxoocta-2,4,6-trienoate. A colourless oil, minor isomer. R_f: 0.27 (hexane/ethyl acetate=4:1). ^{1}H NMR (400 MHz, $CDCl_3$): 10.21 (d, J=7.6 Hz, 1H, C*H*O), 7.53 (d, J=15.1 Hz, 1H, =C*H*), 7.32 (dq, J=11.5, 1.2 Hz, 1H, =C*H*), 6.89 (dd, J=15.1, 11.5 Hz, 1H, =C*H*), 5.97 (d, J=7.6 Hz, 1H, =C*H*), 3.80 (s, 3H, O*Me*), 2.16 (d, J=1.2 Hz, 3H, *Me*), 2.05 (d, J=1.2 Hz, 3H, *Me*). ^{13}C NMR (100 MHz, $CDCl_3$): 189.02, 167.7, 152.4, 136.7, 132.6, 131.4, 130.9, 129.9, 52.4, 21.5, 13.8. HRMS (CI): m/z calculated for $C_{11}H_{14}O_3$ $[M]^+$: 194.0943, found: 194.0947. FTIR (KBr): ν 1764, 1644 (br) cm^{-1}.

4.2.8. (2E,4E,6E)-Methyl 2,6-dimethyl-8-(phenylsulfonyl)octa-2,4,6-trienoate (**9**)

To an oven-dried round-bottom flask equipped with a magnetic stirring bar were added alcohol **7** (500 mg, 2.5 mmol, 1.0 equiv) and Et_2O (20 mL). The mixture was cooled to 0 °C and PBr_3 (0.25 mL, 1.1 equiv, 2.7 mmol) was added. The reaction mixture was gradually warmed to room temperature and was allowed to stir for another 4 h. The mixture was poured into saturated $NaHCO_3$ aqueous solution (50 mL). The aqueous layer was extracted with Et_2O (3×50 mL) and the combined organic layers were washed with

water (50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residual crude product was used without further purification. To an oven-dried round-bottom flask equipped with a magnetic stirring bar was added the crude bromide. The bromide was azeotropically dried with dry THF (2×10 mL). To the round-bottom flask were added $PhSO_2Na$ (0.57 g, 1.3 equiv, 3.2 mmol) and dry DMF (15 mL). The reaction mixture was allowed to stir for another 24 h. The mixture was poured into ice water (30 mL). The aqueous layer was extracted with ethyl acetate (3×40 mL) and the combined organic layers were washed with water (40 mL) and brine (40 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residual crude product was purified by flash column chromatography to afford sulfone **9** in 90% yield as a colourless oil. Isomer ratio=83:17. R_f: 0.13 (hexane/ethyl acetate=4:1). Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$): 7.85–7.82 (m, 2H, =C*H*(Ph)), 7.70–7.60 (m, 1H, =C*H*(Ph)), 7.59–7.46 (m, 2H, =C*H*(Ph)), 7.19 (d, *J*=10.4 Hz, 1H, =C*H*), 6.53–6.32 (m, 2H, C*H*=C*H*), 5.57 (t, *J*=8.4 Hz, 1H, =C*H*–CH_2), 3.97 (d, *J*=8.4 Hz, 2H, CH_2), 3.74 (s, 3H, O*Me*), 1.95 (s, 3H, *Me*), 1.52 (s, 3H, *Me*). ^{13}C NMR (100 MHz, $CDCl_3$): 168.7, 142.2, 141.8, 138.6, 138.0, 133.8, 129.2, 128.4, 128.0, 124.9, 119.7, 56.6, 51.9, 12.9, 12.3. HRMS (CI): *m*/*z* calculated for $C_{17}H_{20}O_4S$ $[M]^+$: 320.1082, found: 320.1094. FTIR (KBr): ν 1703 (br), 1631 (br), 1616, 1554, 1305, 1234, 1149, 1109 cm^{-1}.

4.3. Olefination and imine formation reaction of aldehyde (8)

General procedure. To a round-bottom flask equipped with a magnetic stirring bar were added aldehyde **8** (20 mg, 0.1 mmol, 1.0 equiv), ylide (140 mg, 0.4 mmol, 4.0 equiv) and THF (10 mL). The mixture was refluxed for another 4 h. The mixture was concentrated in vacuo. The residual crude product was purified by flash column chromatography to afford desired product.

*4.3.1. (2E,4E,6E,8E)-Dimethyl 2,5,9-trimethyldeca-2,4,6,8-tetraenedioate (**A**)*

Yield: 80%, yellow solid, mp 125–126 °C. Recrystallization yield: 36%. Isomer ratio=85:15. R_f: 0.50 (hexane/ethyl acetate=4:1). Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$): 7.58 (dd, *J*=12.2, 1.3 Hz, 1H, =C*H*), 7.32–7.22 (m, 1H, =C*H*), 6.70–6.63 (m, 2H, =C*H*), 6.48 (d, *J*=12.2 Hz, 1H, =C*H*), 3.79 (s, 3H, O*Me*), 3.78 (s, 3H, O*Me*), 2.07 (s, 3H, *Me*), 2.02 (s, 6H, *Me*). ^{13}C NMR (100 MHz, $CDCl_3$): 168.9, 168.7, 143.3, 141.7, 138.3, 133.5, 129.2, 128.5, 127.9, 125.6, 52.0, 51.9, 13.0, 12.9, 12.8. HRMS (CI): *m*/*z* calculated for $C_{15}H_{20}O_4$ $[M]^+$: 264.1362, found: 264.1360. FTIR (KBr): ν 1685 (br), 1662 (br), 1618 (br), 1560, 1500 cm^{-1}.

4.3.2. (2E,4E,6E,8E)-Methyl 2,6-dimethyl-9-phenylnona-2,4,6,8-tetraenoate

Yield: 95%, yellow solid, mp 73–74 °C. Isomer ratio=76:24. R_f: 0.75 (hexane/ethyl acetate=4:1). Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$): 7.50–7.45 (m, 2H, =C*H*(Ph)), 7.41–7.25 (m, 3H, =C*H*(Ph)), 7.34 (d, *J*=15.0 Hz, 1H, =C*H*), 7.19 (dd, *J*=15.2, 11.2 Hz, 1H, =C*H*), 6.71 (d, *J*=15.2 Hz, 1H, =C*H*), 6.68 (d, *J*=15.0 Hz, 1H, =C*H*), 6.57 (dd, *J*=15.0, 11.2 Hz, 1H, =C*H*), 6.44 (d, *J*=11.4 Hz, 1H, =C*H*), 3.80 (s, 3H, O*Me*), 2.07 (s, 3H, *Me*), 2.04 (s, 3H, *Me*). ^{13}C NMR (100 MHz, $CDCl_3$): 168.9, 144.0, 139.1, 137.4, 135.7, 135.2, 134.8, 129.2, 128.7, 127.9, 126.6, 125.1, 123.4, 51.8, 12.9, 12.8. HRMS (CI): *m*/*z* calculated for $C_{18}H_{20}O_2$ $[M]^+$: 268.1463, found: 268.1460. FTIR (KBr): ν 1760, 1643 (br), 1635 (br), 1560 cm^{-1}.

4.3.3. (2E,4E,6E,8E)-Methyl 2,6-dimethyldeca-2,4,6,8-tetraenoate

Yield: 95%, yellow solid. Isomer ratio=55:45. R_f: 0.35 (hexane/ethyl acetate=4:1). Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$): 7.20–7.00 (m, 1H, =C*H*), 6.60–6.23 (m, 3H, =C*H*), 5.80 (dq, *J*=13.9, 7.0 Hz, 1H, =C*H*), 6.12 (d, *J*=11.3 Hz, 1H, =C*H*), 3.37 (s, 3H, O*Me*), 1.92 (s, 3H, *Me*), 1.91 (s, 3H, *Me*), 1.78 (d, *J*=7.0 Hz, 3H, *Me*). ^{13}C NMR (100 MHz, $CDCl_3$): 169.1, 144.5, 139.2, 135.1, 132.9, 129.5, 128.2, 125.6, 122.4, 51.7, 13.6, 12.8, 12.5. HRMS (CI): *m*/*z* calculated for $C_{13}H_{18}O_2$ $[M]^+$: 206.1307, found: 206.1306. FTIR (KBr): ν 1707, 1637 (br) cm^{-1}.

4.3.4. (2E,4E,6E,8E,10E)-Methyl 2,6-dimethyl-11-phenylundeca-2,4,6,8,10-pentaenoate

Yield: 91%, yellow solid, mp 113–114 °C. Isomer ratio=83:17. R_f: 0.63 (hexane/ethyl acetate=4:1). ^{1}H NMR (400 MHz, $CDCl_3$): 7.50–7.40 (m, 2H, =C*H*(Ph)), 7.39–7.28 (m, 4H, =C*H* and =C*H* (Ph)), 7.19 (dd, *J*=15.1, 11.3 Hz, 1H, =C*H*), 6.71 (d, *J*=14.5 Hz, 1H, =C*H*), 6.68 (d, *J*=14.5 Hz, 1H, =C*H*), 6.58 (dd, *J*=15.1, 11.1 Hz, 1H, =C*H*), 6.38 (d, *J*=11.1 Hz, 1H, =C*H*), 3.80 (s, 3H, O*Me*), 2.02 (d, *J*=1.0 Hz, 3H, *Me*), 2.02 (s, 3H, *Me*). ^{13}C NMR (100 MHz, $CDCl_3$): 168.9, 143.9, 139.0, 137.3, 135.8, 135.5, 135.1, 133.6, 129.5, 129.3, 128.7, 127.8, 126.5, 126.1, 123.3, 51.8, 12.9, 12.7. HRMS (CI): *m*/*z* calculated for $C_{20}H_{22}O_2$ $[M]^+$: 294.1620, found: 294.1615. FTIR (KBr): ν 1697, 1639 (br), 1568 cm^{-1}.

4.3.5. (2E,4E,6E,8E)-Dimethyl 2,6-dimethyldeca-2,4,6,8-tetraenedioate

Yield: 90%, yellow solid, mp 127–128 °C. Isomer ratio=88:12. R_f: 0.50 (hexane/ethyl acetate=4:1). Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$): 7.69 (dd, *J*=15.1, 12.0 Hz, 1H, =C*H*), 7.28 (dd, *J*=10.8, 1.4 Hz, 1H, =C*H*), 6.70 (dd, *J*=15.1, 10.8 Hz, 1H, =C*H*), 6.60 (d, *J*=15.1 Hz, 1H, =C*H*), 6.33 (d, *J*=12.0 Hz, 1H, =C*H*), 5.98 (d, *J*=15.2 Hz, 1H, =C*H*), 3.78 (s, 3H, O*Me*), 3.78 (s, 3H, O*Me*), 2.08 (s, 3H, *Me*), 2.03 (s, 3H, *Me*). ^{13}C NMR (100 MHz, $CDCl_3$): 168.6, 167.5, 143.2, 142.5, 140.0, 138.0, 131.5, 128.5, 126.4, 122.0, 52.0, 51.6, 13.0, 12.9. HRMS (CI): *m*/*z* calculated for $C_{14}H_{18}O_4$ $[M]^+$: 250.1205, found: 250.1225. FTIR (KBr): ν 1701 (br), 1624 (br) cm^{-1}.

4.3.6. (2E,4E,6E,8E)-Methyl (2,6-dimethyl-8-phenylimino)octa-2,4,6-trienoate

Yield: 88%, red solid, mp 96–97 °C. Isomer ratio=79:21. R_f: 0.25 (hexane/ethyl acetate=4:1). Major isomer: ^{1}H NMR (500 MHz, $CDCl_3$): 8.58 (d, *J*=9.6 Hz, 1H, N=C*H*), 7.41–7.36 (m, 2H, =C*H*), 7.32 (dd, *J*=11.2, 1.2 Hz, 1H, =C*H*), 7.25–7.21 (m, 1H, =C*H*), 7.19–7.16 (m, 2H, =C*H*), 6.80 (dd, *J*=15.2, 11.2 Hz, 1H, =C*H*), 6.71 (d, *J*=15.2 Hz, 1H, =C*H*), 6.53 (d, *J*=9.9 Hz, 1H, =C*H*), 3.81 (s, 3H, O*Me*), 2.22 (s, 3H, *Me*), 2.06 (s, 3H, *Me*). ^{13}C NMR (100 MHz, $CDCl_3$): 168.6, 157.9, 152.2, 145.7, 142.4, 137.8, 133.0, 129.2, 129.1, 127.0, 126.3, 121.0, 52.0, 13.2, 13.1. HRMS (CI): *m*/*z* calculated for $C_{17}H_{19}NO_2$ $[M]^+$: 269.1416, found: 269.1410. FTIR (KBr): ν 1633 (br), 1516 cm^{-1}.

4.3.7. (2E,4E,6E,8E)-Methyl 8-((1R,2S)-1-hydroxy-1-phenylpropan-2-ylimino)-2,6-dimethylocta-2,4,6-trienoate

Yield: 95%, yellow solid, mp 85–86 °C. Recrystallization yield: 45%. Isomer ratio=86:14. Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$): 8.29 (d, *J*=9.6 Hz, 1H, N=C*H*), 7.41–7.33 (m, 6H, =C*H* and =C*H*(Ph)), 6.74 (dd, *J*=15.2, 11.2 Hz, 1H, CH=C*H*), 6.61 (d, *J*=15.2 Hz, 1H, CH=C*H*), 6.29 (d, *J*=9.3 Hz, 1H, C*H*–C=N), 4.78 (d, *J*=4.4 Hz, 1H, OC*H*), 3.80 (s, 3H, O*Me*), 3.53–3.45 (m, 1H, C*H*–Me), 2.60 (br, 1H, O*H*), 2.07 (s, 3H, *Me*), 2.04 (s, 3H, *Me*), 1.14 (d, *J*=6.2 Hz, 3H, *Me*–CH). ^{13}C NMR (100 MHz, $CDCl_3$): 168.7, 158.8, 143.7, 141.3, 137.9, 132.2, 128.6, 128.2, 128.1, 127.4, 126.6, 126.5, 126.3, 77.0, 71.8, 52.0, 16.3, 13.0, 12.9. HRMS (CI): *m*/*z* calculated for $C_{20}H_{25}NO_3$ $[M]^+$: 327.1834, found: 327.1835. FTIR (KBr): ν 3435 (br), 1720, 1625 (br), 1556 cm^{-1}.

4.4. Elongation of 8-methoxy-8-oxo-dehydrogeranal (8)

*4.4.1. (E)-4-Hydroxyprenyl acetate (**11**)*

To a round-bottom flask equipped with a magnetic stirring bar were added prenyl acetate (25.6 g, 200 mmol, 1.0 equiv), SeO_2 (22.2 g, 200 mmol, 1.0 equiv) and ethanol (250 mL, 95%). The mixture was heated at reflux for 24 h. The mixture was diluted with ethyl acetate (100 mL). The organic layer was washed with brine (3×50 mL). The organic layer was dried over anhydrous Na_2SO_4,

filtered and concentrated in vacuo until 40 mL liquid was left. The mixture was cooled to 0 °C and $NaBH_4$ (1.9 g, 50 mmol, 0.25 equiv) was added slowly. The reaction was stirred for another 12 h. The mixture was diluted with ethyl acetate (100 mL). The organic layer was washed with water (50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residual crude product was purified by flash column chromatography to afford desired product **11** in 42% yield as a colourless oil. R_f: 0.13 (hexane/ethyl acetate=4:1). ^{1}H NMR (300 MHz, $CDCl_3$): 5.63 (t, J=5.1 Hz, 1H, =C*H*), 4.65 (d, J=5.1 Hz, 2H, CH_2–OAc), 4.06 (s, 2H, CH_2–OH), 2.06 (s, 3H, C(O)–*Me*), 1.73 (s, 3H, *Me*). ^{13}C NMR (75 MHz, $CDCl_3$): 170.1, 140.8, 118.6, 67.7, 60.9, 21.0, 13.8. HRMS (CI): m/z calculated for $C_7H_{12}O_3$ $[M]^+$: 144.0860, found: 144.0856. FTIR (KBr): ν 1739, 1645 (br) cm^{-1}.

4.4.2. (E)-4-Diethoxyphosphorylprenyl acetate (**12**)

To an oven-dried round-bottom flask equipped with a magnetic stirring bar were added alcohol **11** (12.1 g, 84 mmol, 1.0 equiv), pyridine (8.9 mL, 109 mmol, 1.3 equiv) and DMF (200 mL). The mixture was cooled to 0 °C and $MeSO_2Cl$ (7.80 mL, 101 mmol, 1.2 equiv) was added via syringe. The reaction mixture was gradually warmed to room temperature and was stirred for another 6 h. The mixture was poured into ice water (100 mL). The aqueous layer was extracted with ethyl acetate (3×50 mL) and the combined organic layers were washed with aqueous HCl (50 mL, 0.3 M), water (50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residual crude product was used for the next step without purification. The mixture was transferred into a round-bottom flask and $P(OEt)_3$ (14.6 mL, 84 mmol, 1.0 equiv) was added via syringe. The reaction mixture was heated at 150 °C for 24 h. The residual crude product was purified by flash column chromatography to afford desired product **12** in 60% yield as a colourless oil. R_f: 0.13 (ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): 5.51 (q, J=6.8 Hz, 1H, =C*H*), 4.61 (dd, J=7.1, 4.3 Hz, 2H, CH_2–OAc), 4.16–4.05 (m, 4H, O–*CH*$_2$–Me), 2.59 (d, J=22.2 Hz, 2H, CH_2–P), 2.04 (s, 3H, C(O)–*Me*), 1.87 (d, J=2.9 Hz, 3H, =C–*Me*), 1.31 (t, J=7.1 Hz, 6H, OCH_2–*Me*). ^{13}C NMR (75 MHz, $CDCl_3$): 170.8, 132.6 (d, J=10.9 Hz), 123.5 (d, J=13.0 Hz), 61.9 (d, J=5.3 Hz), 60.8, 36.8 (d, J=136.3 Hz), 20.8 (d, J=5.7 Hz), 17.6 (d, J=3.0 Hz), 16.3 (d, J=4.9 Hz). HRMS (CI): m/z calculated for $C_{11}H_{22}O_5P$ $[M+H]^+$: 265.1205, found $[M+H]^+$: 265.1200. FTIR (KBr): ν 1739, 1647 (br), 1236, 1068 cm^{-1}.

4.4.3. (E)-4-Diethoxyphosphorylprenol (**13**)

To an oven-dried round-bottom flask equipped with a magnetic stirring bar were added ester **12** (530 mg, 2.0 mmol, 1.0 equiv) and toluene (6 mL). The mixture was cooled −78 °C and DIBAL-H (1.0 M in heptane, 4 mL, 2.0 mmol, 2.0 equiv) was added via syringe. The reaction mixture was stirred for another 12 h at −78 °C. The mixture was poured into ice water (20 mL) and potassium and sodium tartrate saturated solution (20 mL). The aqueous layer was extracted with ethyl acetate (3×50 mL). The organic layers were combined and dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residual crude product was purified by flash column chromatography to afford desired product **13** in 52% yield as a colourless oil. R_f: 0.07 (ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): 5.58 (q, J=6.8 Hz, 1H, =C*H*), 4.18 (t, J=5.7 Hz, 2H, CH_2–OH), 4.15–4.05 (m, 4H, O–*CH*$_2$–Me), 2.57 (d, J=22.1 Hz, 2H, P–CH_2), 1.83 (d, J=3.2 Hz, 3H, =C–*Me*), 1.32 (t, J=6.8 Hz, 6H, CH$_2$–*Me*). ^{13}C NMR (100 MHz, $CDCl_3$): 129.3 (d, J=13.0 Hz), 129.0, 62.0 (d, J=7.3 Hz), 58.8, 36.6 (d, J=136.4 Hz), 17.5 (d, J=2.9 Hz), 16.4 (d, J=5.9 Hz). HRMS (CI): m/z calculated for $C_9H_{19}O_4P$ $[M]^+$: 222.1021, found: 222.1020. FTIR (KBr): ν 3427 (br), 1647, 1211, 1053, 970 cm^{-1}.

4.4.4. (E)-4-Diethoxyphosphorylprenal (**14**)

To a round-bottom flask equipped with a magnetic stirring bar were added alcohol **13** (222 mg, 1.0 mmol, 1.0 equiv) and DMSO (5 mL). The mixture was cooled to 0 °C and IBX (560 mg, 2.0 mmol, 2.0 equiv) was added. The reaction mixture was gradually warmed to room temperature and was allowed to stir for another 30 min. Then the mixture was poured into ice water (30 mL). The aqueous layer was extracted with ethyl acetate (3×50 mL) and the combined organic layers were washed with brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residual crude product was purified by flash column chromatography to afford desired product **14** in 80% yield as a colourless oil. Isomer ratio=96:4. R_f: 0.30 (ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): 9.99 (d, J=7.8 Hz, 1H, C*H*O), 5.96 (t, J=7.8 Hz, 1H, =C*H*), 4.13 (quintet, J=7.2 Hz, 4H, O–CH_2), 2.75 (d, J=23.9 Hz, 2H, P–CH_2), 2.33 (dd, J=3.6, 1.2 Hz, 3H, =C–*Me*), 1.33 (t, J=7.2 Hz, 6H, O–CH$_2$–*Me*). ^{13}C NMR (75 MHz, $CDCl_3$): 190.4 (d, J=3.7 Hz), 153.7 (d, J=11.1 Hz), 130.7 (d, J=11.0 Hz), 62.4 (d, J=6.6 Hz), 40.8, 38.4 (d, J=133.5 Hz), 18.7 (d, J=2.7 Hz), 16.3 (d, J=6.1 Hz). HRMS (CI): m/z calculated for $C_9H_{17}O_4P$ $[M]^+$: 220.0865, found: 220.0862. FTIR (KBr): ν 2984, 2931, 2908, 1682, 1635, 1029, 967 cm^{-1}.

4.4.5. (2E,4E,6E,8E,10E)-Methyl 2,6,10-trimethyl-12-oxododeca-2,4,6,8,10-pentaenoate ((2E,4E,6E,8E,10E)-12-methoxy-12-oxo-dehydrofarnesal) (**15**)

To an oven-dried round-bottom flask equipped with a magnetic stirring bar were added alcohol **14** (110 mg, 0.5 mmol, 2.5 equiv), $BnNH_2$ (54 mg, 0.5 mmol, 2.5 equiv) and THF (5 mL). The mixture was stirred for 30 min before THF was azeotropically removed. The reaction mixture was azeotropically dried with dry THF (2×5 mL). To the reaction mixture MS 4 Å (0.1 g) and THF (3 mL) were added. The reaction mixture was cooled to −78 °C before LiHMDS (1.0 M in THF, 0.5 mL, 0.5 mmol, 2.5 equiv) was added. The reaction mixture was stirred for 10 min at −78 °C before a THF (1.0 mL) solution of aldehyde **8** (39 mg, 0.2 mmol, 1.0 equiv) was added via syringe. The reaction mixture was gradually warmed to room temperature and was allowed to stir for another 12 h. The mixture was poured into ice water (20 mL). The aqueous layer was extracted with ethyl acetate (3×250 mL) and the combined organic layers were washed with water (20 mL) and brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residual crude product was purified by flash column chromatography to afford desired product **15** in 75% yield as a yellow solid, mp 123–124 °C. Isomer ratio=96:4. R_f: 0.20 (hexane/ethyl acetate=4:1). Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$): 10.12 (d, J=8.1 Hz, 1H, C*H*O), 7.32–7.25 (m, 1H, =C*H*), 7.11 (dd, J=15.1, 11.4 Hz, 1H, =C*H*), 6.70–6.57 (m, 2H, =C*H*), 6.47 (d, J=15.1 Hz, 1H, =C*H*), 6.37 (d, J=11.4 Hz, 1H, =C*H*), 6.01 (d, J=8.1 Hz, 1H, =C*H*), 3.78 (s, 3H, O*Me*), 2.34 (d, J=0.9 Hz, 3H, *Me*), 2.06 (s, 3H, *Me*), 2.02 (d, J=1.2 Hz, 3H, *Me*). ^{13}C NMR (100 MHz, $CDCl_3$): 191.1, 168.7, 154.0, 143.0, 139.9, 138.3, 136.9, 133.8, 131.6, 129.9, 127.7, 125.4, 51.8, 13.0, 13.0, 12.9. HRMS (CI): m/z calculated for $C_{16}H_{20}O_3$ $[M]^+$: 260.1412, found: 260.1419. FTIR (KBr): ν 1701, 1660, 1647, 1616, 1595 cm^{-1}.

4.4.6. (2E,4E,6E,8E,10E,12E,14E)-Methyl 2,6,10,14-tetramethyl-16-oxohexadeca-2,4,6,8,10,12,14-heptaenoate ((2E,4E,6E,8E,10E,12E,14E)-16-methoxy-16-oxo-dehydrogeranylgeranal) (**16**)

To an oven-dried round-bottom flask equipped with a magnetic stirring bar were added alcohol **14** (88 mg, 0.4 mmol, 7.0 equiv), $BnNH_2$ (43 mg, 0.4 mmol, 7.0 equiv) and THF (5 mL). The mixture was stirred for 30 min before THF was azeotropically removed. The reaction mixture was azeotropically dried with dry THF (2×5 mL). To the reaction mixture MS 4 Å (0.1 g) and THF (3 mL) were added. The reaction mixture was cooled to −78 °C before LiHMDS (1.0 M in THF, 0.4 mL, 0.4 mmol, 7.0 equiv) was added. The reaction mixture was stirred for 10 min at −78 °C before a THF (1.0 mL) solution of aldehyde **15** (16 mg, 0.06 mmol, 1.0 equiv) was added via syringe. The reaction mixture was gradually warmed to room temperature

and was stirred for another 12 h. The mixture was poured into ice water (20 mL). The aqueous layer was extracted with ethyl acetate (3×250 mL) and the combined organic layers were washed with water (20 mL) and brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residual crude product was purified by flash column chromatography to afford desired product in 85% yield as a dark red solid, mp 81–82 °C. Isomer ratio=72:28. R_f: 0.28 (hexane/ethyl acetate=4:1). Major isomer: ^{1}H NMR (500 MHz, $CDCl_3$): 10.11 (d, *J*=8.1 Hz, 1H, C*H*O), 7.29 (dd, *J*=10.5, 1.0 Hz, 1H, =C*H*), 7.11 (dd, *J*=14.8, 11.5 Hz, 1H, =C*H*), 6.76 (dd, *J*=14.8, 11.5 Hz, 1H, =C*H*), 6.63 (d, *J*=14.8 Hz, 1H, =C*H*), 6.56 (dd, *J*=15.1, 11.1 Hz, 1H, =C*H*), 6.46 (d, *J*=11.2 Hz, 1H, =C*H*), 4.41 (d, *J*=11.2 Hz, 1H, =C*H*), 6.34 (d, *J*=10.5 Hz, 1H, =C*H*), 6.30 (d, *J*=11.1 Hz, 1H, =C*H*), 6.98 (d, *J*=8.1 Hz, 1H, =C*H*), 3.77 (s, 3H, O*Me*), 2.33 (s, 3H, *Me*), 2.05 (s, 3H, *Me*), 2.01 (s, 3H, *Me*), 2.00 (s, 3H, *Me*). ^{13}C NMR (125 MHz, $CDCl_3$): 191.1, 168.9, 154.3, 143.8, 140.8, 139.0, 138.8, 136.8, 135.9, 135.3, 132.2, 132.1, 129.5, 126.8, 126.4, 123.7, 51.8, 13.1, 13.1, 12.9, 12.9. HRMS (CI): *m*/*z* calculated for $C_{21}H_{26}O_3$ $[M]^+$: 326.1882, found: 326.1881. FTIR (KBr): ν 1647, 1635 (br) cm^{-1}.

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Supplementary data

Copies of ^{1}H NMR and ^{13}C spectrums for compounds **3**–**9**, **11**–**16**, products of Table 1 and X-ray data for compound **A** are available. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.03.094.

References and notes

1. Ravi, B. N.; Well, R. J.; Croft, K. D. *J. Org. Chem.* **1981**, *46*, 1998–2001.
2. (a) Clement, J. A.; Li, M.; Hecht, S. M.; Kingston, D. G. I. *J. Nat. Prod.* **2006**, *69*, 373–376; (b) Liu, W. K.; Cheung, F. W. K.; Che, T. C. *J. Nat. Prod.* **2006**, *69*, 934–937; (c) Lv, F.; Deng, Z. W.; Li, J.; Fu, H. Z.; van Soest, R. W. M.; Proksch, P.; Lin, W. H. *J. Nat. Prod.* **2004**, *67*, 2033–2036; (d) Tasdemir, D.; Mangalindan, G. C.; Concepción, G. P.; Verbitski, S. M.; Rabindran, S.; Miranda, M.; Greenstein, M.; Hooper, J. N. A.; Harper, M. K.; Ireland, C. M. *J. Nat. Prod.* **2002**, *65*, 210–214; (e) Meragelman, K. M.; McKee, T. C.; Boyd, M. R. *J. Nat. Prod.* **2001**, *64*, 389–392; (f) Che, C. T.; Zhang, W. H. *J. Nat. Prod.* **2001**, *64*, 1489–1492; (g) McKee, T. C.; Bokesch, H. R.; McCormick, J. L.; Rashid, M. A.; Spielvogel, D.; Gustafson, K. R.; Alavanja, M. M.; Cardellina, J. H., II; Boyd, M. R. *J. Nat. Prod.* **1997**, *60*, 431–438; (h) Rao, Z. G.; Deng, S. Z.; Wu, H. M.; Jiang, S. K. *J. Nat. Prod.* **1997**, *60*, 1163–1164; (i) Su, J. Y.; Meng, Y. H.; Zeng, L. M. *J. Nat. Prod.* **1994**, *57*, 1450–1451.
3. Jackson, H. L.; Nadolski, G. T.; Braun, C.; Lockwood, S. F. *Org. Process Res. Dev.* **2005**, *9*, 830–836 and references therein.
4. (a) Stewart, M.; Capon, R. J.; Lacey, E.; Tennant, S.; Gill, J. H. *J. Nat. Prod.* **2005**, *68*, 581–584 and references therein; (b) Tatsuta, K.; Itoh, M.; Hirama, R.; Araki, N.; Kitagawa, M. *Tetrahedron Lett.* **1997**, *38*, 583–586.
5. Reviews for carotenoids and related nature products synthesis: (a) Valla, A. R.; Cartier, D. L.; Labia, R. *Curr. Org. Synth.* **2004**, *1*, 167–209; (b) Pfander, H.; Traber, B.; Lanz, M. *Pure Appl. Chem.* **1997**, *69*, 2047–2060; (c) Mercier, C.; Chabardes, P. *Pure Appl. Chem.* **1994**, *66*, 1509–1518; (d) Paust, J. *Pure Appl. Chem.* **1991**, *63*, 45–58; (e) Bernhard, K.; Mayer, H. *Pure Appl. Chem.* **1991**, *63*, 35–44; (f) Widmer, E. *Pure Appl. Chem.* **1985**, *57*, 741–752; (g) Isler, O. *Pure Appl. Chem.* **1979**, *51*, 447–462; (h) Weedon, B. C. L. *Pure Appl. Chem.* **1976**, *47*, 161–171; (i) Pommer, H. *Angew. Chem.* **1960**, *72*, 911–915; (j) Vaz, B.; Alvarez, R.; Bruckner, R.; de Lera, A. R. *Org. Lett.* **2005**, *7*, 545–548; (k) Vaz, B.; Domínguez, M.; Álvarez, R.; de Lera, A. R. *J. Org. Chem.* **2006**, *71*, 5914–5920; (l) Fürstner, A.; Nevado, C.; Waser, M.; Tremblay, M.; Chevrier, C.; Teplý, F.; Aïssa, C.; Moulin, E.; Müller, O. *J. Am. Chem. Soc.* **2007**, *129*, 9150–9161.
6. (a) Koskinen, A. *Asymmetric Synthesis of Natural Products*; Wiley: Chichester, UK, 1993; pp 168–191; (b) Cane, D. E. *Comprehensive Natural Products Chemistry*; Barton, D., Nakanishi, K., Eds.; Elsevier: Oxford, 1999; Vol. 2; pp 1–13.
7. For reviews of conjugated polyene synthesis, see: (a) Thirsk, C.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2002**, *24*, 999–1023; (b) Negishi, E.; Hu, Q.; Huang, Z. H.; Qian, M. X.; Wang, G. W. *Aldrichimica Acta* **2005**, *38*, 71–88; For recent development in conjugated polyene synthesis, see: (c) Batsanov, A. S.; Knowles, J. P.; Whiting, A. *J. Org. Chem.* **2007**, *72*, 2525–2532; (d) Ebran, J. P.; Hansen, A. L.; Gøgsig, T. M.; Skrydstrup, T. *J. Am. Chem. Soc.* **2007**, *129*, 6931–6942; (e) Coleman, R. S.; Lu, X. L.; Modolo, I. *J. Am. Chem. Soc.* **2007**, *129*, 3826–3827; (f) Coleman, R. S.; Walczak, M. C. *Org. Lett.* **2005**, *7*, 2289–2291; (g) Coleman, R. S.; Walczak, M. C.; Campbell, E. L. *J. Am. Chem. Soc.* **2005**, *127*, 16038–16039 and references therein; (h) Hoffmann, R. W.; Rohde, T.; Haeberlin, E.; Schafer, F. *Org. Lett.* **1999**, *1*, 1713–1715; (i) Mapp, A. K.; Heathcock, C. H. *J. Org. Chem.* **1999**, *64*, 23–27; (j) Andrus, M. B.; Lepore, S. D. *J. Am. Chem. Soc.* **1997**, *119*, 2327–2328 and references therein; (k) Murakami, Y.; Nakano, M.; Shimofusa, T.; Furuichi, N.; Katsumura, S. *Org. Biomol. Chem.* **2005**, *3*, 1372–1374.
8. (a) Jeon, H. S.; Koo, S. *Tetrahedron Lett.* **2004**, *45*, 7023–7026; (b) Ji, M.; Choi, H.; Park, M.; Kee, M.; Jeong, Y. C.; Koo, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 3627–3629.
9. (a) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526–5528; (b) Reley, H. L.; Morley, J. F.; Friend, N. A. C. *J. Chem. Soc.* **1932**, 1875.
10. CCDC 665102 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data.request/cif.
11. Kann, N.; Rein, T.; Akermark, B.; Helquist, P. *J. Org. Chem.* **1990**, *55*, 5312–5323.
12. (a) Liu, X. H.; Prestwich, G. D. *J. Am. Chem. Soc.* **2002**, *124*, 20–22; (b) Meinwald, J.; Opheim, K. *Tetrahedron Lett.* **1973**, *14*, 281–284.