Supporting Information for:

Synthesis of Hydroxy-α-sanshool

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**General Experimental Procedures**

All reagents were obtained from the Acros, Aldrich, Alfa Aesar or Lancaster chemical companies, and were used as received. $^1$H-, $^{13}$C-, and $^{31}$P-NMR spectra were recorded in CDCl$_3$ on a Bruker DRX-400 spectrometer operating at 400 MHz for $^1$H analysis, 100 MHz for $^{13}$C analysis, and 162 MHz for $^{31}$P analysis respectively. Proton chemical shift data is expressed in ppm with reference to TMS. EI-MS data was recorded on a Finnigan MAT 96 mass spectrometer. Melting points were determined using Stuart Scientific SMP1 melting point apparatus. The E:Z alkene isomer ratios were determined using an HPLC system equipped with a Waters 1525 binary pump and 3100 mass detector.
**Synthetic Procedures**

**4-Bromobutanal (9).** To a solution of 4-bromobutan-1-ol (28.9 g, 189 mmol) in CH₂Cl₂ (200 mL) at r.t., was added pyridinium chlorochromate (44.8 g, 208 mmol) in portions. After the addition was complete, the mixture was stirred at r.t. for 1.5 h, and then silica gel (50 g) was added. The solvent was removed in vacuo, and diethyl ether (200 mL) was then added. The resulting mixture was filtered, and the filter cake was washed with additional diethyl ether (200 mL). The combined filtrate was concentrated in vacuo, and the crude product was distilled under reduced pressure to afford 9 (21.7 g, 76% yield) as a colorless oil. ¹H-NMR (400 MHz, CDCl₃) δ ppm 2.15-2.22 (m, 2H), 2.67-2.71 (m, 2H), 3.47 (t, J = 6.4 Hz, 2H), 9.82 (s, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ ppm 25.4, 33.2, 42.5, 201.2; MS for C₄H₉BrO: calcd 151.0, found 151.0.

**Methyl 6-Bromo-2E-hexenoate (5).** A solution of methyl (triphenylphosphoranylidene)acetate (8, 52.9 g, 158 mmol) in CH₂Cl₂ (80 mL) was added dropwise at r.t. to 9 (21.7 g, 144 mmol), and the mixture was stirred at r.t. overnight. The solvent was removed in vacuo, and then resulting residue was triturated with hexane (200 mL) and filtered. The filter cake was washed with additional hexane (200 mL), and the combined filtrate was concentrated in vacuo. The crude product was distilled under reduced pressure to afford 5 (27.1 g, yield 91%) as a colorless oil (E:Z = 92:8). ¹H-NMR (400MHz, CDCl₃) δ ppm 1.99-2.06 (m, 2H), 2.36-2.42 (m, 2H), 3.42 (t, J = 6.6 Hz,
(2H), 3.74 (s, 3H), 5.89 (dt, \(J_1 = 15.6 \text{ Hz}, J_2 = 1.6 \text{ Hz}, 1\text{H}\)), 6.93 (dt, \(J_1 = 15.2 \text{ Hz}, J_2 = 6.8 \text{ Hz}, 1\text{H}\)); \(^{13}\text{C-NMR (100 MHz, CDCl}_3\)) \(\delta\) ppm 30.8, 31.2, 32.9, 51.9, 122.6, 147.5, 167.2; MS for \(\text{C}_7\text{H}_{11}\text{BrO}_2\): calcd 206.0, found 206.0.

**6-Methoxy-6-oxo-4E-hexenyl)triphenylphosponium bromide (10).** A mixture of 5 (20.7 g, 100 mmol) and PPh\(_3\) (28.9 g, 110 mmol) in acetonitrile (100 mL) was refluxed overnight. The solvent was removed *in vacuo* and the crude product was triturated with diethyl ether (200 mL) and stirred for 15 min. The insoluble white powder was filtered, washed with diethyl ether (100 mL), and dried *in vacuo* to afford 10 (45.1 g, yield 96%) as white solid (m.p. = 130-131 °C). \(^1\text{H-NMR (400 MHz, CDCl}_3\)) \(\delta\) ppm 1.74-1.84 (m, 2H), 2.02 (s, 1H), 2.71 (dd, \(J_1 = 14.4 \text{ Hz}, J_2 = 7.2 \text{ Hz}, 2\text{H}\)), 3.69 (s, 1H), 3.93-4.00 (m, 2H), 5.85 (d, \(J = 15.6 \text{ Hz}, 2\text{H}\)), 6.78-6.86 (m, 1H), 7.69-7.74 (m, 6H), 7.79-7.89 (m, 9H); \(^{13}\text{C-NMR (100 MHz, CDCl}_3\)) \(\delta\) ppm 21.8 (d, \(J_{\text{PC}} = 4.0 \text{ Hz}\)), 22.6 (d, \(J_{\text{PC}} = 49.7 \text{ Hz}\)), 32.6 (d, \(J_{\text{PC}} = 17.3 \text{ Hz}\)), 51.9, 118.5 (d, \(J_{\text{PC}} = 84.7 \text{ Hz}\)), 122.9, 131.0 (d, \(J_{\text{PC}} = 13.3 \text{ Hz}\)), 134.1 (d, \(J_{\text{PC}} = 9.5 \text{ Hz}\)), 135.5 (d, \(J_{\text{PC}} = 2.7 \text{ Hz}\)), 147.5, 167.4; \(^{31}\text{P-NMR (162 MHz, CDCl}_3\)) \(\delta\) ppm 24.5; MS (FAB) for \(\text{C}_{25}\text{H}_{26}\text{O}_2\text{P}^+\): calcd 389.2, found 389.2.

**Methyl 2E,6Z,8E,10E-dodecatetraenoate (11).** A mixture of 10 (28.2 g, 60 mmol), \(\text{K}_2\text{CO}_3\) (16.6 g, 120 mmol) and 6 (8.7 g, 90 mmol) in toluene (120 mL) was stirred at 70 °C under a
nitrogen atmosphere overnight. After cooling to r.t. the mixture was filtered, the filter cake was washed with hexane (100 mL), and the combined filtrate was concentrated in vacuo. The crude product was triturated again with hexane, filtered and concentrated in vacuo to afford 11 (9.9 g, yield 80%) as a yellow oil (2E,6Z:2E,6E:2Z,6Z = 59:31:10). $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ ppm 1.78 (d, $J = 6.8$ Hz, 3H), 2.27-2.38 (m, 4H), 3.72 (s, 3H), 5.32-5.43 (m, 1H), 5.69-5.77 (m, 1H), 5.85 (d, $J = 16.0$ Hz, 1H), 6.00-6.21 (m, 3H), 6.29-6.55 (m, 1H), 6.98 (dt, $J_1 = 15.6$ Hz, $J_2 = 6.8$ Hz, 1H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ ppm 18.3, 26.3, 32.3, 51.5, 121.5, 125.2, 129.2, 129.9, 130.2, 131.9, 133.7, 148.5, 166.9. MS for C$_{13}$H$_{18}$O$_2$: calc 206.1, found 206.1.

2E,6Z,8E,10E-dodecatetraenoic acid (2). A mixture of 11 (2.1 g, 10 mmol) and NaOH (2.0 g, 50 mmol) in water (20 mL) was stirred at 70 °C for 3 h. After cooling to r.t. the reaction mixture was extracted with diethyl ether, and then acidified with aqueous HCl (1 M) to pH = 1. The organic layer was washed with brine, dried over MgSO$_4$, filtered, and concentrated in vacuo to afford a white solid. The crude product was recrystallized from 1% ethyl acetate in hexane to afford 2 (0.8 g, yield 43%) as a white solid (m.p. = 94-95 °C, 2E,6Z:2E,6E:2Z,6Z = 96:2:2). $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ ppm 1.78 (d, $J = 6.8$ Hz, 3H), 2.32-2.38 (m, 4H), 5.35 (dd, $J_1 = 14.4$ Hz, $J_2 = 7.2$ Hz, 1H), 5.74 (dq, $J_1 = 20.8$ Hz, $J_2 = 10.4$ Hz, 1H), 5.85 (d, $J = 14.4$ Hz, 1H), 6.04 (d, $J = 10.8$ Hz, 1H), 6.09-6.22 (m, 2H), 6.29-6.35 (m, 1H), 7.08 (dt, $J_1 = 15.6$ Hz, $J_2 = 6.4$ Hz, 1H);
$^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ ppm 18.4, 26.2, 32.4, 121.3, 125.2, 129.1, 130.0, 130.4, 131.9, 133.8, 151.3, 172.3. MS for C$_{12}$H$_{16}$O$_2$: calcd 192.1, found 192.1.

(2E,6Z,8E,10E)-N-(2-hydroxy-2-methylpropyl)dodeca-2,6,8,10-tetraenamide (1).  To a mixture of 2 (0.4 g, 2 mmol), 3$^2$ (0.3 g, 3 mmol) and triethylamine (0.6 mL, 4 mmol) in MeCN (4 mL) and CHCl$_3$ (2 mL), was added HBTU (1.1 g, 3 mmol). After 20 min the reaction was judged to be complete by TLC analysis (EA:hexane = 1:1). The reaction mixture was diluted with diethyl ether (50 mL), and washed with brine, 1N HCl, water, 5% NaHCO$_3$, and brine. The organic layer was dried over MgSO$_4$, filtered, and concentrated in vacuo to afford 1 (0.5 g, yield 92%) as a colorless oil. $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ ppm 1.21 (s, 6H), 1.76 (d, $J$ = 7.2 Hz, 3H), 2.23-2.35 (m, 4H), 3.13 (s, 1H), 3.30 (d, $J$ = 6.0 Hz, 2H), 5.34 (dd, $J_1$ = 14.4 Hz, $J_2$ = 7.2 Hz, 1H), 5.85 (d, $J$ = 15.2 Hz, 1H), 6.00 (dd, $J_1$ = 21.6 Hz, $J_2$ = 10.8 Hz, 1H), 6.19-6.06 (m, 2H), 6.27-6.33 (m, 2H), 6.84 (dt, $J_1$ = 13.2 Hz, $J_2$ = 6.4 Hz, 1H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ ppm 18.4, 26.5, 27.2, 32.1, 50.6, 70.8, 124.0, 125.2, 129.4, 129.7, 130.2, 131.8, 133.6, 144.1, 167.2. HRMS for C$_{16}$H$_{25}$NO$_2$: calcd 263.1885, found 263.1879.
References:

