Supporting Information
for
Stereoselective synthesis of hernandulcin, peroxylippidulcine A, lippidulcines A, B and C and taste evaluation

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Experimental procedures, analytical data, and copies of $^1$H and $^{13}$C NMR spectra of all compounds

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1. General Information

$^1$H and $^{13}$C NMR spectra were recorded on a Bruker 400 or 500 DRX spectrometer in CDCl$_3$ solutions at room temperature using residual CHCl$_3$ or TMS as internal reference for $^1$H and CDCl$_3$ for $^{13}$C, chemical shifts are expressed in ppm and $J$ values in Hz. GC–MS analyses were performed on an Agilent HP 6890 gas-chromatograph equipped with a 5973 mass detector and an Agilent HP-5 (30 m × 0.25 mm × 0.25 μm) column. Temperature program: 60 °C (1 min) / 6 °C min$^{-1}$ / 150 °C (1 min) / 12 °C min$^{-1}$ / 280 °C (5 min). Optical rotations were determined on a Dr. Kernchen Propol digital automatic polarimeter at 589 nm and are given in °cm$^3$ g$^{-1}$ dm$^{-1}$ at rt. Thin layer chromatography (TLC) analyses were performed on Merck Kieselgel 60 F$_{254}$ plates, and column chromatographic separations were carried out on silica gel. All reagents and solvents were purchased from Sigma-Aldrich. The reagents were used without further purification, while where required the solvents were anhydricated with molecular sieves. All the ADHs employed were purchased from Sigma-Aldrich except those from C. parapsilosis and R. erythropolis which were purchased from Jülich.
2. Experimental procedures and analytical data

(S)-Isopulegone

To an ice cold and well stirred solution of (-)-isopulegol (31.0 g, 0.2 mol) in acetone (300 mL) was added dropwise the Jones reagent (2.8 M, 93.0 mL, 0.26 mol, 1.3 equiv). The reaction mixture was stirred for 3 h, until no further conversion was observed. Then, the reaction mixture was quenched with NaHCO$_3$ (1 M, 150 mL). The slurry was filtered on a celite pad; the latter was washed with EtOAc (3 x 50 mL). The filtrate was concentrated under reduced pressure and diluted with Et$_2$O (200 mL), washed with brine (3 x 50 mL), dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure to afford the crude product as a yellow-green liquid. Column chromatographic separation (eluent n-hexane/EtOAc, 95:05) gave (S)-isopulegone as colourless liquid (16.2 g); 53% yield; $R_f$ = 0.43 (9:1, n-hexane/EtOAc); $t_r$ = 10.67 min 99% purity by GC; 95% de by NMR; $[\alpha]_D$ = −10.1° (c 2.0, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 4.86 (quin, $J$ = 1.5 Hz, 1H), 4.65 (sep, $J$ = 1.7, 0.8 Hz, 1H), 2.89 (dd, $J$ = 12.9, 5.4 Hz, 1H), 2.33 (ddd, $J$ = 13.3, 3.9, 2.2 Hz, 1H), 2.03 − 1.94 (m, 2H), 1.91 − 1.76 (m, 2H), 1.73 (dd, $J$ = 13.0, 3.4 Hz, 1H), 1.69 (dd, $J$ = 1.4, 0.9 Hz, 3H), 1.37 (tdd, $J$ = 12.5, 11.1, 3.3 Hz, 1H), 0.98 (d, $J$ = 6.3 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 209.79, 143.48, 112.71, 57.69, 50.54, 35.27, 33.86, 31.21, 22.26, 21.26; GC/MS: $m/z$ (%) 152 (M$^+$, 25), 137 (20), 67 (100).

(+)-Neoisopulegone (4)

Method A

To an ice cold solution of DIBAL-H in THF (1.8 M, 5.5 mL, 10 mmol, 1 equiv) under a nitrogen atmosphere was added dropwise a solution of 2-propanol (0.75 mL, 10
mmol, 1 equiv) in toluene (2.0 mL) and then left at rt for 1 h. Then, the reaction mixture was ice cooled and the (S)-isopulegone (1.5 g, 10 mmol) was slowly added, left at 0 °C for 3 h and then for 3 h at rt. 10% conversion and 0% de was obtained.

**Method B**

To a solution of (S)-Isopulegone (6.5 g, 42.7 mmol) in THF (130 mL) under a N₂ atmosphere at −78 °C was added dropwise a solution of L-Selectride in THF (1.0 M, 64.0 mL, 64.0 mmol, 1.5 equiv). The reaction temperature was left to reach rt in about 2 hours. After stirring for 14 h the mixture was cooled to 0 °C and H₂O₂ (30 wt %, 22.0 mL, 170 mmol, 4 equiv) was slowly added, followed by aqueous NaOH (15 mL, 15 wt.%) and stirred overnight at rt. The organic layer was washed with brine (3 × 30 mL), dried over Na₂SO₄ and the solvent removed under reduced pressure to afford a yellowish crude liquid. Column chromatographic separation (eluent n-hexane/EtOAc, 98:2) gave 4 as colourless liquid (5.5 g); 84% yield; Rᵣ=0.52 (8:2 n-hexane/EtOAc); tᵣ = 10.21 min 99% by GC; 96.7% de by NMR; [α]₀ = +24.5° (c 2.0, CHCl₃) vs. lit.¹ [α]₀ = +28.7° (c 17.2, CHCl₃) or distomer² [α]₀ = −22.2° (c 2.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 4.90 (dq, J = 2.1, 1.0 Hz, 1H), 4.75 (s, 1H), 3.95 (s, 1H), 1.98 – 1.88 (m, 2H), 1.84 – 1.62 (m, 6H), 1.52 (s, 1H), 1.46 – 1.37 (m, 1H), 1.14 – 1.04 (m, 1H), 0.97 – 0.88 (m, 1H), 0.85 (d, J = 6.5 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 147.42, 111.22, 66.50, 48.58, 41.20, 34.92, 25.86, 24.07, 22.74, 22.28; GC/MS: m/z (%) 154 (M⁺, 15), 136 (50), 121 (100). Anal. Calcd for C₁₀H₁₈O: C, 77.87; H, 11.76. Found: C, 77.84; H, 11.72.
**Method C**

To a phosphate buffer solution (50 mM, 850 μL, pH 7) were added (S)-isopulegone (770 μg, 5 μmol) in DMSO (10 μL), glucose (20 μL, 1 M sol), NAD(P)+ (10 μL, 10 mM sol., see Table 1), the ADH (see Table 1), the GDH-BM (30 μL, 1.0 mg/mL sol.). The reaction was stirred for 24 h at 30 °C, then extracted with EtOAc (1.0 mL), dried over Na2SO4 and submitted to GC–MS analysis (Table 1).

**Method D**

To an ice cold mixture and well stirred mixture of (−)-isopulegol (24.0 g, 156 mmol), p-nitrobenzoic acid (52.0 g, 0.31 mol, 2 equiv) and PPh3 (82.0 g, 0.31 mol, 2 equiv) in toluene (160 mL) was added dropwise DIAD (64.0 g, 312 mmol, 2 equiv). The reaction mixture was stirred at rt for 24 h, then it was filtered at -10 °C and the solid was washed with n-hexane (3 × 50 mL). The organic phase was extracted with brine (3 × 100 mL). The combined aqueous layers were extracted with Et2O (3 × 50 mL). The combined organic layers were dried over Na2SO4 and the solvent removed under reduced pressure to afford a yellowish crude solid. Crystallization of PPh3O, with n-hexane (100 mL), at 0 °C, allowed the purification of crude ester which was used for the next step without further purification; 87% yield; tR = 26.22 min 91% purity by GC; [a]D = +37.6° (c 1.4, CHCl3); 1H NMR (400 MHz, CDCl3) δ 8.34 – 8.10 (m, 4H), 5.56 (dd, J = 3.7, 2.3 Hz, 1H), 4.83 – 4.64 (m, 2H), 2.18 – 2.04 (m, 2H), 1.98 – 1.85 (m, 2H), 1.83 – 1.69 (m, 5H), 1.36 – 1.24 (m, 1H), 1.17 – 1.02 (m, 1H), 0.93 (d, J = 6.6 Hz, 3H); 13C NMR (125 MHz, CDCl3) δ 164.01, 150.47, 145.93, 136.43, 130.73, 123.65, 111.20, 72.38, 47.00, 39.27, 34.58, 27.11, 25.40, 22.64, 22.23;
GC/MS: m/z (%) 303 (M⁺, 1), 167 (8), 150 (63), 79 (100). Anal. Calcd for C₁₇H₂₁NO₄: C, 67.31; H, 6.98. Found: C, 67.32; H, 6.92.

To a water cooled and well stirred solution of the above ester (45.4 g, 136 mmol) in MeOH (200 mL) was added slowly a MeONa solution (0.68 M, 200 mL, 136 mmol, 3 equiv) over 1 h. Then the reaction mixture was allowed to reach rt and stirred for other 4 h. The reaction was concentrated under reduced pressure (100 mL), then it was added ice cold brine (400 mL). The mixture was filtered and the solid washed with MeOH (3 × 50 mL). The filtrate was washed with CH₂Cl₂ (3 × 200 mL) and the combined organic layers were washed with brine (2 × 100 mL), dried over Na₂SO₄ and the solvent was removed under reduced pressure to afford a yellowish liquid. Column chromatographic separation (eluent n-hexane/EtOAc, 95:5) gave 4 as colourless liquid (20.1 g); 96% yield; 97.5% purity by GC; >99% de by NMR and GC; [α]D = +25° (c 2.0, CHCl₃) vs. lit.¹ [α]D = +28.7° (c 17.2, CHCl₃) or distomer² [α]D = −22.2° (c 2.0, CHCl₃).

(1S,2S,5R)-5-Methyl-2-(6-methylhepta-1,5-dien-2-yl)cyclohexanol (5)

To an ice cooled solution of 4 (19.0 g, 123 mmol) in n-hexane (400 mL) under a N₂ atmosphere was quickly added t-BuOK (13.8 g, 123 mmol, 1 equiv) and left to stir at rt for 15 min. Therefore n-BuLi (2.5 M, 150 mL, 370 mmol, 3 equiv) was added dropwise at −10 °C. After 2 h freshly-clear-distilled prenyl bromide (17.8 mL, 154 mmol, 1.25 equiv) was added drop by drop, and the reaction was left to stir for 45 min at −10 °C, then at rt for 15 min. The reaction was quenched at 0 °C with brine (300 mL, starting drop by drop until no more gases are generated) until all solid were dissolved. Then the organic layer was separated and the aqueous layer was extracted with Et₂O (3 × 100 mL). The combined organic layers were washed with brine (2 × 100 mL) and the brine extracted with Et₂O (50 mL). Finally, the combined organic layers were dried over Na₂SO₄ and the solvent removed under reduced pressure. Column chromatographic separation (eluent n-hexane/EtOAc in gradient, from n-hexane to 98:2) gave 5 as colourless liquid (23.0 g); 84% yield; tₑ= 20.10 min
96% purity by GC; \( R_t = 0.5 \) (9:1, n-hexane/EtOAc); 96% de by NMR; \([\alpha]_D = +19.5^\circ \) (c 1.2, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 5.09 (tdq, \( J = 5.8, 3.0, 1.5 \) Hz, 1H), 4.94 (t, \( J = 1.5 \) Hz, 1H), 4.83 (s, 1H), 3.91 (q, \( J = 2.8 \) Hz, 1H), 2.21 – 1.91 (m, 6H), 1.86 – 1.69 (m, 3H), 1.67 (d, \( J = 1.4 \) Hz, 3H), 1.60 (d, \( J = 1.3 \) Hz, 3H), 1.57 – 1.51 (m, 1H), 1.45 – 1.34 (m, 1H), 1.10 (dddd, \( J = 13.6, 12.2, 2.7, 1.4 \) Hz, 1H), 1.04 – 0.90 (m, 1H), 0.87 (d, \( J = 6.5 \) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 151.43, 131.92, 124.00, 110.45, 66.45, 47.46, 41.13, 36.04, 35.09, 26.85, 25.91, 25.73, 24.35, 22.34, 17.80; GC/MS: \( m/z \) (%) 222 (M\(^+\), 5), 204 (22), 161 (75), 69 (100); Anal. Calcd for C\(_{15}\)H\(_{26}\)O\(_2\): C, 81.02; H, 11.79. Found: C, 81.07; H, 11.75.

\((1S,2R,5R)-5\)-Methyl-2-((S)-2-(4-methylpent-3-enyl)oxiran-2-yl)cyclohexanol (6)

\[
\begin{align*}
\text{5} & \quad \text{VO(acac)}_2 \\
& \quad \text{TBHP} \\
\rightarrow & \quad \text{6}
\end{align*}
\]

To a water cold solution of 5 (13.7 g, 61.7 mmol) and VO(acac)\(_2\) (300 mg) in toluene (300 mL) under a N\(_2\) atmosphere was added dropwise a solution of TBHP in toluene (4.87 m, 15.2 g, 74 mmol, 1.2 equiv) over 30 min. After 12 h was added PPh\(_3\) (3.2 g, 12.3 mmol, 0.2 equiv), and after 5 minutes the solvent was removed under reduced pressure. Column chromatographic purification (eluent n-hexane/EtOAc gradient, n-hexane up to 95:5) gave 6 as colourless liquid (13.9 g); 95% yield; \( t_r = 22.00 \) min 96% purity by GC; \( R_t = 0.32 \) (8:2, n-hexane/EtOAc); 95% de by NMR; \([\alpha]_D = +34.2^\circ \) (c 1.3, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 5.13 – 5.01 (m, 1H), 4.33 (s, 1H), 2.91 (s, 1H), 2.84 – 2.44 (m, 2H), 2.06 – 1.78 (m, 5H), 1.77 – 1.70 (m, 2H), 1.69 (dd, \( J = 5.9, 1.6 \) Hz, 3H), 1.60 (s, 3H), 1.48 (dddd, \( J = 20.0, 15.8, 13.2, 5.6 \) Hz, 2H), 1.38 – 1.23 (m, 2H), 1.08 – 0.90 (m, 2H), 0.86 (d, \( J = 6.5 \) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 132.38, 123.46, 67.89, 63.32, 49.61, 41.92, 41.56, 35.68, 34.88, 25.78, 25.67, 23.75, 22.93, 22.33, 17.80; GC/MS: \( m/z \) (%) 238 (M\(^+\), 1), 220 (22), 95 (78), 69 (100); Anal. Calcd for C\(_{15}\)H\(_{26}\)O\(_2\): C, 75.58; H, 10.99. Found: C, 75.57; H, 11.01.
To an ice cold and well stirred solution of 6 (15.4 g, 64.5 mmol) in dry THF (250 mL) was added dropwise under a N₂ atmosphere a solution of LiAlH₄ (2.8 g, 71.5 mmol, 1.1 equiv) in dry THF (100 mL) over 45 min. The reaction mixture was stirred until no further conversion was observed after 4 h. Then, the slurry was quenched with a Signette salt solution (sat., 350 mL), filtered and the solid washed with CH₂Cl₂ (3 × 100 mL). The aqueous phase was washed with CH₂Cl₂ (3 × 100 mL). The combined organic phase was washed with the Signette salt solution (sat., 100 mL), brine (sat., 2 × 100 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure to give a yellow crude liquid. After crystallization (n-hexane, −70 °C to −30 °C) 7 was afforded as white solid (13.1 g); 85% yield; tᵣ = 22.59 min purity >99% by GC; Rᵣ=0.19 (9:1, n-hexane/EtOAc); 96% de by NMR; [α]D = +7.28° (c 1.2, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 5.14 (tdq, J = 7.1, 2.9, 1.4 Hz, 1H), 4.33 (s, 1H), 3.40 (d, J = 2.3 Hz, 1H), 3.05 (s, 1H), 1.95 (ddq, J = 19.4, 14.1, 7.5, 7.0 Hz, 2H), 1.78 (ddq, J = 18.1, 9.7, 5.1, 4.2 Hz, 4H), 1.60 (d, J = 13.0 Hz, 9H), 1.20 (dt, J = 12.4, 3.0 Hz, 1H), 1.14 (s, 3H), 0.98 (d, J = 15.0 Hz, 1H), 0.87 (td, J = 12.9, 3.7 Hz, 1H), 0.84 (d, J = 6.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 131.57, 124.53, 75.28, 67.73, 46.24, 42.71, 41.31, 35.17, 25.75, 25.71, 25.30, 23.37, 22.27, 20.29, 17.70. GC/MS: m/z (%) 222 (M⁺-18, 18), 204 (50), 189 (40), 109 (100). Anal. Calcd for C₁₅H₂₈O₂: C, 74.95; H, 11.74. Found: C, 74.90; H, 11.72.
(2S,5R)-2-((S)-2-Hydroxy-6-methylhept-5-en-2-yl)-5-methylcyclohexanone (8)

To an ice cold and stirred solution of 7 (1.00 g, 4.16 mmol) in CH₂Cl₂ (20 mL) was added portion wise DMP (2.12 g, 5 mmol, 1.2 equiv). After 1h the reaction was left to stir overnight at rt. Then it was added n-hexane/Et₂O (1:1, 40 mL), the slurry was filtrated and the filtrate was washed with NaHCO₃ (sat., 2 × 10 mL) and brine (sat., 10 mL), and finally dried over Na₂SO₄. The solvent was removed under reduced pressure. Column chromatographic separation (eluent, n-hexane/EtOAc gradient: n-hexane up to 8:2) gave 8 as a colourless liquid (0.88 g); 90% yield; Rᵣ=0.55 (7:3, n-hexane/EtOAc); 8 decomposes into GC column into 3-methylcyclohexanone and 6-methyl-5-hepten-2-one; 96.3% de by NMR; [α]D = +11.0° (c 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 5.06 (dddd, J = 8.6, 5.7, 2.9, 1.5 Hz, 1H), 3.92 (s, 1H), 2.44 – 2.27 (m, 2H), 2.12 – 1.75 (m, 6H), 1.64 (q, J = 1.3 Hz, 3H), 1.58 (d, J = 1.3 Hz, 3H), 1.55 – 1.39 (m, 3H), 1.31 (tdd, J = 12.9, 11.2, 3.5 Hz, 1H), 1.14 (s, 3H), 0.99 (d, J = 6.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 215.29, 131.43, 131.43, 124.68, 73.02, 56.87, 51.63, 40.56, 35.43, 34.07, 28.51, 25.72, 23.79, 22.29, 22.07, 17.66; Anal. Calcd for C₁₅H₂₆O₂: C, 75.58; H, 10.99. Found: C, 75.61; H, 10.94.

(2S,5R)-5-Methyl-2-((S)-6-methyl-2-(trimethylsilyloxy)hept-5-en-2-yl)cyclohexanone (9)

To a water cold and stirred solution of 8 (3.14 g, 13.2 mmol) in CH₂Cl₂/pyridine (2:1, 30 mL) was added dropwise TMSCl (3.6 g, 33 mmol, 2.5 equiv) under a N₂ atmosphere. After 13 h, to the reaction mixture at 0 °C was added drop by drop brine (sat., 50 mL). Then the slurry was filtered, the solid washed with CH₂Cl₂ (2 × 20 mL)
and the aq. phase extracted with CH$_2$Cl$_2$ (3 × 50 mL). The combined organic phase was dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure. Column chromatographic separation (eluent n-hexane/EtOAc +1% Et$_3$N, gradient: n-hexane to 95:5) gave 9 as colourless liquid (4.05 g); 98.9% yield; $R_f$ = 0.75 (7:3 n-hexane/EtOAc); $t_r$ = 22.49 min 96.2% purity by GC; $[\alpha]_D$ = -11.5° (c 1.3, CHCl$_3$) vs. lit.$^3$ $[\alpha]_D$ = -16.3° (c 0.12, EtOH); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.10 (ddq, $J$ = 8.6, 5.8, 1.5 Hz, 1H), 2.39 (ddd, $J$ = 12.7, 5.0, 1.2 Hz, 1H), 2.30 (ddd, $J$ = 12.5, 4.3, 2.1 Hz, 1H), 2.20 (ddt, $J$ = 13.2, 5.0, 3.4 Hz, 1H), 2.06 – 1.80 (m, 5H), 1.74 – 1.64 (m, 4H), 1.63 – 1.59 (m, 3H), 1.52 (qd, $J$ = 12.8, 3.2 Hz, 1H), 1.44 – 1.22 (m, 5H), 0.99 (d, $J$ = 6.3 Hz, 3H), 0.10 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 210.74, 131.02, 125.23, 76.66, 60.66, 52.14, 38.70, 35.98, 34.49, 27.86, 25.87, 25.79, 22.56, 22.38, 17.69, 2.72; GC/MS: $m/z$ (%) 220 (M$^+$$-$H$_2$OTMS, 32), 295 (M$^+$$-$Me, 5), 185 (38), 109 (100). Anal. Calcd for C$_{18}$H$_{34}$O$_2$Si: C, 69.62; H, 11.04. Found: C, 69.61; H, 11.07.

**General procedure for the preparation of silylenolether 10a and 10**

To a stirred solution of diisopropylamine (1.62 g, 16 mmol, 1.6 equiv) in dry THF (10 mL) at −30 °C was added dropwise n-BuLi (2.5 M, 5.6 mL, 14 mmol, 1.4 equiv) under a N$_2$ atmosphere keeping the temperature below -25° C. The reaction was left at rt for 10 min. To the reaction mixture at -78 °C was added dropwise a solution of 9 (3.11 g, 10 mmol) in dry THF (10 mL) keeping the temperature below -73 °C during the addition. After 90 min at -78 °C a solution of R$_3$SiCl (13 mmol, 1.3 equiv) in dry THF (10 mL) was added dropwisely in such a way to keep the temperature below -73 °C. After 90 min at -78 °C the reaction mixture was left to reach rt. Then, at -30 °C a phosphate buffer solution (1 M, 30 mL, 7.1 pH) was added. Then, it was filtrated on celite pad, the solid was washed with CH$_2$Cl$_2$ (2 × 10 mL). The aq. phase was washed with CH$_2$Cl$_2$ (3 × 30 mL). The combined organic phase was dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure to afford a yellow liquid.
Trimethyl((S)-6-methyl-2-((1S,4R)-4-methyl-2-(trimethylsilyloxy)cyclohex-2-enyl)hept-5-en-2-yloxy)silane (10)

In this case the product as yellow liquid (3.49 g) was of sufficient purity for the next step; 91% yield; \( R_t = 22.95 \text{ min} \) 95% purity by GC; 95% de; \([\alpha]_D = +19.7^\circ \text{ (c 1.4, CHCl}_3\text{)}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta 5.12 \) (tp, \( J = 7.1, 1.5 \text{ Hz} \), 1H), 4.70 (p, \( J = 1.0 \text{ Hz} \), 1H), 2.26 (dddd, \( J = 9.7, 6.6, 3.1, 1.4 \text{ Hz} \), 1H), 2.15 (ddtd, \( J = 11.4, 9.5, 4.8, 2.6 \text{ Hz} \), 1H), 2.07 – 1.94 (m, 2H), 1.88 – 1.71 (m, 2H), 1.68 (q, \( J = 1.2 \text{ Hz} \), 3H), 1.61 (d, \( J = 1.2 \text{ Hz} \), 3H), 1.57 – 1.26 (m, 7H), 0.92 (d, \( J = 6.9 \text{ Hz} \), 3H), 0.19 (s, 9H), 0.11 (s, 9H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta 151.03, 130.56, 125.52, 113.94, 78.37, 49.99, 38.02, 31.68, 30.21, 29.07, 25.66, 25.17, 22.77, 22.69, 17.55, 2.58, 0.27. \) GC/MS: \( m/z \) (%): 382 (M\(^+\)-1, 1), 367 (M\(^+\)-Me, 2), 69 (40), 199 (100). Anal. Calcd for C\(_{21}\)H\(_{42}\)O\(_2\)Si\(_2\): C, 65.90; H, 11.06. Found: C, 65.91; H, 11.04.

Triethyl((3R,6S)-3-methyl-6-((S)-6-methyl-2-(trimethylsilyloxy)hept-5-en-2-yly)cyclohex-1-enyloxy)silane (10a)

Column chromatographic separation (eluent n-hexane (+1% Et\(_3\)N)) gave 10a as colourless liquid 3.48 g; 82% yield; \( R_t = 25.46 \text{ min} \) 96.1% purity by GC; \([\alpha]_D = +16.6^\circ \text{ (c 1.2, CHCl}_3\text{)}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta 5.12 \) (dddd, \( J = 8.6, 5.7, 2.8, 1.4 \text{ Hz} \), 1H), 4.70 (dt, \( J = 2.1, 1.0 \text{ Hz} \), 1H), 2.29 (ddddd, \( J = 9.6, 6.8, 3.0, 1.4 \text{ Hz} \), 1H), 2.25 – 2.11 (m, 1H), 2.11 – 1.95 (m, 2H), 1.88 – 1.71 (m, 2H), 1.68 (q, \( J = 1.3 \text{ Hz} \), 3H), 1.61 (d, \( J = 1.2 \text{ Hz} \), 3H), 1.55 – 1.47 (m, 2H), 1.45 (s, 3H), 0.98 (q, \( J = 7.8 \text{ Hz} \), 11H), 0.92 (d, \( J = 6.9 \text{ Hz} \), 3H), 0.75 – 0.67 (m, 6H), 0.12 (s, 9H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta 151.46, 130.68, 125.82, 113.02, 78.72, 50.38, 38.10, 31.82, 30.43, 29.51, 25.82, 25.32, 22.98, 22.94, 17.69, 6.96, 5.32, 2.75. \) GC/MS: \( m/z \) (%): 409 (M\(^+\)-Me, 1), 334 (2), 69 (40), 199 (100). Anal. Calcd for C\(_{24}\)H\(_{48}\)O\(_2\)Si\(_2\): C, 67.86; H, 11.39. Found: C, 67.84; H, 11.43.
Method A: Saegusa–Ito oxidation of 10

A mixture of Pd(OAc)₂ (700 mg, 3.13 mmol, 0.3 equiv) in dry DMSO (120 mL) was heated at 58 °C and stirred for 30 min in a Schlenk tube. Then, 10 (4.0 g, 10.4 mmol) was added, and O₂ was bubbled into the apparatus, which was shielded against sunlight. After 24 h it was added more catalyst (470 mg, 2.1 mmol, 0.2 equiv) and the reaction was bubbled for additional 2 days. Then, at rt was added a solvent mixture of n-hexane/Et₂O (3:7, 120 mL). The reaction mixture was filtrated on a pad of celite, the solid was washed with Et₂O (3 × 40 mL), the filtrate was washed with brine (sat., 200 mL). The aqueous phase was washed with n-hexane/Et₂O (3:7, 3 × 100 mL), the combined organic phase was washed with brine (sat., 4 × 30 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure to afford a dark crude oil. Column chromatographic separation (eluent n-hexane/EtOAc, 9:1 +0.1% Et₃N) gave 11 as a colourless liquid (1.74 g); 54% yield; tᵣ = 23.41 min 96% purity by GC; Rᵣ=0.40 (9:1 n-hexane/EtOAc); [α]₀ = +11.1° (c 1.4, CHCl₃) vs. lit.³ [α]₀ = +9.7° (c 0.14, EtOH)); ¹H NMR (400 MHz, CDCl₃) δ 5.76 (h, J = 1.3 Hz, 1H), 5.08 (ddq, J = 8.5, 5.8, 1.4 Hz, 1H), 2.45 – 2.24 (m, 2H), 2.23 – 2.12 (m, 2H), 2.11 – 2.00 (m, 1H), 2.00 – 1.89 (m, 2H), 1.88 (d, J = 1.3 Hz, 3H), 1.73 – 1.66 & 1.43 – 1.34 (ddd, 2H), 1.64 (q, J = 1.2 Hz, 3H), 1.59 (d, J = 1.3 Hz, 3H), 1.44 (s, 3H), 0.07 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 199.90, 160.42, 131.04, 128.20, 124.99, 77.83, 54.83, 39.50, 31.14, 27.39, 25.71, 24.28, 23.84, 23.32, 17.66, 2.66; GC/MS: m/z (%) 308 (M⁺, 1), 293 (M⁺-Me, 15), 225 (63), 109 (100); Anal. Calcd for C₁₈H₃₂O₂Si: 70.07; H, 10.45. Found: 70.09; H, 10.48.
Method B: Saegusa–Ito oxidation of 10a

A mixture of 10a (1.75 g, 4.12 mmol) and Pd(OAc)$_2$ (277 mg, 1.24 mmol, 0.3 equiv) in a mixed solvent system of dry DMSO/MeCN/CH$_2$Cl$_2$ (2:2:1, 250 mL) at 50 °C was bubbled with O$_2$ for 7 days in a Schlenk tube. During this time it was added occasionally more catalyst and CH$_2$Cl$_2$. Then, the work-up was made as in the previous case. 4% yield; the spectroscopic and GC data are consistent with that obtained with Method A.

(+)-Hernandulcin (1)

To a water cold and stirred solution of 11 (308 mg, 1 mmol) in MeCN (5 mL) was added TBAF (1 M, 2 mL, 2 mmol, 2 equiv) and the reaction was stirred at rt for 2 h. The reaction mixture diluted with Et$_2$O (20 mL), washed with brine (2 × 10 mL), dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure. Column chromatographic separation (eluent n-hexane/EtOAc gradient: n-hexane up to 9:1) gave 1 as an slight orange-yellow liquid (220 mg); 92% yield; $R_t$=0.52 (1:1 n-hexane/EtOAc); 1 decomposes into the GC-MS$^4$ in 3-methyl-2-cyclohexen-1-one and 6-methyl-5-hepten-2-one; $[\alpha]_D = +130^\circ$ (c 1.6, CHCl$_3$) vs. lit.$^5$ $[\alpha]_D = +115^\circ$ (c 0.64, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.83 (dq, $J = 3.1$, 1.4 Hz, 1H), 5.13 (t, $J = 1.4$ Hz, 1H), 5.08 (tdq, $J = 7.1$, 2.9, 1.4 Hz, 1H), 2.43 – 2.20 (m, 3H), 2.19 – 2.07 (m, 1H), 2.07 – 1.95 (m, 2H), 1.92 (t, $J = 1.2$ Hz, 3H), 1.72 – 1.61 (m, 1H), 1.64 (d, $J = 1.3$ Hz, 3H), 1.58 (d, $J = 1.3$ Hz, 3H), 1.44 (ddd, $J = 9.0$, 7.7, 1.3 Hz, 2H), 1.13 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 203.95, 163.28, 131.39, 127.64, 124.71, 73.93, 52.38,
40.33, 31.40, 25.69, 25.20, 24.03, 23.70, 21.69, 17.66; Anal. Calcd for C_{15}H_{24}O_{2}: C, 76.23; H, 10.24. Found: C, 76.25; H, 10.22.

**Peroxyllipidulcines A, B and C (2a–c)**

![Chemical structure](image)

To a solution of 1 (1.1 g, 4.66 mmol) in CH\(_2\)Cl\(_2\) (400 mL) and MeOH (100 mL) was bubbled O\(_2\) in presence of methylene blue (3 drops, alcoholic sat. solution) and the reaction vessel was irradiated with white light for 15 h. Then, the solvent was removed under reduced pressure. The crude material was diluted with Et\(_2\)O/n-hexane (1:1, 200 mL), washed with brine (sat., 10 × 5 mL), dried over Na\(_2\)SO\(_4\) and the solvent was removed under reduced pressure to afford a yellowish liquid 2 (1.2 g). 96% yield; R\(_f\)=0.13 (7:3 n-hexane/EtOAc); [α]\(_D\) of mixture = +90.9° (c 1.5, CHCl\(_3\)); 2a-c decompose into the GC-MS\(^4\),^1H NMR (400 MHz, CDCl\(_3\)) δ 9.47 (s, hydroperoxide 2b 20.4%), 9.42 (s, hydroperoxide 2c 32.3%), 8.83 (s, hydroperoxide 2a 47.3%); ^13C NMR (100 MHz, CDCl\(_3\)) δ 204.27 (s, hydroperoxide 2a 45%), 204.13 (s, hydroperoxide 2c 34%), 204.03 (s, hydroperoxide 2b 21%), 164.15, 164.10, 143.99, 137.25, 127.43, 127.39, 126.18, 113.55, 113.51, 89.06, 88.89, 81.81, 74.56, 74.34, 65.81, 52.50, 51.97, 51.89, 43.24, 35.57, 35.42, 31.31, 25.02, 24.96, 24.84, 24.54, 24.31, 24.16, 24.06, 23.82, 23.74, 23.26, 17.84, 15.18.

**Photooxygenation followed by DeLaMare rearrangement**

**Method A (12 + 13)**

![Chemical structure](image)
To a stirred solution of 2 (0.9 g, 3.36 mmol) in dry DMF (15 mL) was added imidazole (460 mg, 6.7 mmol, 2 equiv), TBDPSCI (930 mg, 3.36 mmol, 1 equiv) and then a catalytic amount of DMAP (20 mg). Reaction was kept stirred at rt for 24 h, then the reaction mixture was ice-cooled and brine (sat., 15 mL) was added drop by drop. The reaction was diluted with n-hexane/Et₂O (7:3, 100 mL), extracted with brine (3 × 10 mL), HCl (1 M, 7 mL), brine (sat., 10 mL), NaHCO₃ (sat., 10 mL) and brine (sat., 10 mL). Finally, the combined organic phase was dried over Na₂SO₄. The solvent was removed under reduced pressure. Column chromatographic separation (eluent n-hexane/EtOAc in gradient: from n-hexane to 6:4) gave 12 as a yellowish solid (0.35 g mg) and 13 as a yellowish liquid (0.15 g).

(S)-6-((S,E)-6-(tert-Butyldiphenylsilylperoxy)-2-hydroxy-6-methylhept-4-en-2-yl)-3-methylcyclohex-2-enone (12). Yield 43%; Rᵣ=0.34 (7:3, n-hexane/EtOAc); 12 decomposes into the GC-MS⁴; ¹H NMR (400 MHz, CDCl₃) δ 7.81 – 7.67 (m, 4H), 7.47 – 7.28 (m, 6H), 5.85 (ddd, J = 16.0, 9.1, 5.3 Hz, 1H), 5.79 (q, J = 1.5 Hz, 1H), 5.60 (ddd, J = 16.0, 1.8, 0.8 Hz, 1H), 2.35 (dd, J = 13.8, 4.5 Hz, 1H), 2.29 – 2.07 (m, 2H), 2.06 – 1.98 (m, 2H), 1.97 – 1.83 (m, 2H), 1.79 (d, J = 1.2 Hz, 3H), 1.74 – 1.37 (m, 3H), 1.32 (d, J = 8.3 Hz, 6H), 1.29 (dt, J = 2.8, 1.4 Hz, 3H), 1.16 (s, 3H), 1.12 (s, 9H), 0.94 – 0.86 (m, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 204.37, 163.58, 137.27, 135.91, 135.88, 134.97, 133.68, 129.78, 127.81, 127.56, 126.27, 82.94, 74.34, 51.60, 43.63, 31.70, 31.16, 27.56, 25.23, 24.87, 24.41, 24.18, 24.02, 22.76, 19.75, 14.18; Anal. Calcd for C₃₁H₄₂O₄Si: C, 73.47; H, 8.35. Found: C, 73.42; H, 8.39.

(S)-6-((S)-2-hydroxy-6-methyl-5-oxohept-6-en-2-yl)-3-methylcyclohex-2-enone (13). Yield 34%; Rᵣ=0.14 (7:3, n-hexane/EtOAc); 12 decomposes into the GC-MS⁴; ¹H NMR (400 MHz, CDCl₃) δ 5.97 (t, J = 1.0 Hz, 1H), 5.81 (t, J = 1.8 Hz, 1H), 5.69 (t, J = 1.1 Hz, 1H), 5.25 (d, J = 1.3 Hz, 1H), 2.90 – 2.68 (m, 2H), 2.39 – 2.20 (m, 3H), 2.03 (dt, J = 13.1, 4.6, 2.7 Hz, 1H), 1.90 (t, J = 1.2 Hz, 3H), 1.81 (t, J = 1.2 Hz, 3H), 1.77 – 1.70 (m, 2H), 1.70 – 1.56 (m, 1H), 1.11 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 203.64, 202.32, 163.66, 144.41, 127.46, 124.46, 73.55, 52.80, 34.46, 31.43, 31.35, 25.05, 24.00, 23.22, 17.64; Anal. Calcd for C₁₅H₂₂O₃: C, 71.97; H, 8.86. Found: C, 72.03; H, 8.97.
Method B (15a + 14)

To an ice cooled solution of 2 (0.65 g, 2.43 mmol) in CH$_2$Cl$_2$/Pyridine (2:1, 12 mL) was added TMSCl (1.85 mL, 14.6 mmol, 6 equiv) and DMAP (20 mg). The reaction was stirred for 4 h at 0 °C, and then left at rt for 20 h (the reaction has to be monitored by $^1$H NMR and not by TLC, since the acidity of SiO$_2$ cleaves the peroxy silyl group). The reaction mixture was quenched with distilled water at 0 °C, diluted with n-hexane/Et$_2$O (10:1, 220 mL) and washed with HCl (0.5 M, 2 × 10 mL) until acid pH of the extract, then with brine (sat., 10 mL). The organic phase was dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure. Then to a water cooled solution of the crude material in CH$_2$Cl$_2$ (2 mL) was added slowly PPh$_3$ (0.65 g, 2.48 mmol, 1.02 equiv) and the reaction was stirred for 15 min at rt. Then, to the reaction mixture diluted with CH$_2$Cl$_2$ (20 mL) was added MnO$_2$ (6.5 g, 10 equiv in wt.) and the reaction was stirred at rt 1 h. The reaction was filtered over celite and the solvent was removed under reduced pressure. Column chromatographic separation (eluent n-hexane/EtOAc in gradient: from n-hexane to 6:4) gave in order elution 14 as a transparent liquid (295 mg), and 15a as a transparent liquid (305 mg).

(S)-3-methyl-6-((S)-6-methyl-5-oxo-2-(trimethylsilyloxy)hept-6-en-2-yl)cyclohex-2-enone (14). Yield 71%; $R_{f}$=0.45 (7:3, n-hexane/EtOAc); $t_r$= 24.81 min >99% purity by GC; [α]$_D$ = +13.6° (c 1.1, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 6.02 (t, J = 0.9 Hz, 1H), 5.79 (dt, J = 1.8, 1.2 Hz, 1H), 5.76 (qd, J = 1.5, 0.8 Hz, 1H), 2.82 (ddd, J = 15.7, 10.6, 5.9 Hz, 1H), 2.65 (ddd, J = 15.7, 10.4, 5.1 Hz, 1H), 2.47 – 2.36 (m, 1H), 2.31 (dd, J = 10.1, 4.5 Hz, 1H), 2.27 – 2.14 (m, 2H), 2.03 – 1.93 (m, 1H), 1.93 – 1.89 (m, 3H), 1.86 (dd, J = 1.5, 0.9 Hz, 3H), 1.85 – 1.74 (m, 2H), 1.48 (s, 3H), 0.09 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 202.24, 199.61, 160.82, 144.55, 128.06, 124.35, 77.36, 55.33, 33.84, 33.11, 31.24, 27.34, 24.14, 23.84, 17.75, 2.60; GC/MS: m/z (%) 309 (M$^+$, 44), 225 (21), 213 (31), 75 (100); Calcd for C$_{18}$H$_{30}$O$_3$Si: C, 67.03; H, 9.38. Found: C, 67.24; H, 9.46.
(S)-6-((S,E)-6-hydroxy-6-methyl-2-(trimethylsilyloxy)hept-4-en-2-yl)-3-methylcyclohex-2-enone (15a). Yield 82%. $R_f=0.18$ (7:3, n-hexane/EtOAc); $t_r=24.27$ min 97% purity by GC; $[\alpha]_D = -11.3^\circ$ (c 1.0, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 5.79 (q, $J = 1.4$ Hz, 1H), 5.69 – 5.65 (m, 2H), 2.51 – 2.38 (m, 2H), 2.27 (dd, $J = 8.8$, 4.7 Hz, 1H), 2.18 (td, $J = 4.1$, 2.9 Hz, 2H), 2.15 (dd, $J = 5.8$, 3.3 Hz, 2H), 2.02 – 1.93 (m, 1H), 1.90 (p, $J = 0.9$ Hz, 3H), 1.41 (s, 3H), 1.31 – 1.29 (m, 6H), 0.09 – 0.07 (m, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 199.99, 160.65, 141.32, 128.17, 123.39, 77.84, 70.67, 53.97, 42.82, 30.93, 29.91, 29.80, 27.62, 24.23, 23.84, 2.61; GC/MS: $m/z$ (%) 309 (M$^+$, 6), 225 (37), 213 (5), 75 (100); Anal. Anal. Calcd for C$_{18}$H$_{32}$O$_3$Si: C, 66.62; H, 9.94. Found: C, 66.57; H, 10.03.

Peroxylippidulcine A (2a)

To a solution of 12 (0.51 g, 1.01 mmol) in THF (5 mL) was added TBAF (1 M, 2 mL, 2.02 mmol, 2 equiv) and reaction was kept stirred at rt for 12 h. The reaction mixture diluted with Et$_2$O (50 mL), washed with brine (sat., 3 × 5 mL), dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure. Column chromatographic separation (eluent n-hexane/EtOAc in gradient: from n-hexane to 6:4) gave peroxylippidulcine A 2a as a yellowish solid 224 mg; 83% yield; $R_f=0.06$ (7:3 n-hexane/EtOAc); $[\alpha]_D = +43.5^\circ$ (c 1.6, CHCl$_3$) vs. lit.$^6$ $[\alpha]_D = +42.0^\circ$ (c 3.2, CHCl$_3$); 2a decomposes into the GC-MS$^4$; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.38 (s, 1H), 5.89 – 5.70 (m, 2H), 5.60 (dt, $J = 16.0$, 1.3 Hz, 1H), 5.35 (t, $J = 1.3$ Hz, 1H), 2.38 (dd, $J = 13.9$, 4.5 Hz, 1H), 2.34 – 2.25 (m, 2H), 2.25 – 2.11 (m, 2H), 2.01 (td, $J = 12.9$, 4.6, 2.7 Hz, 1H), 1.93 (t, $J = 1.1$ Hz, 3H), 1.69 – 1.57 (m, 1H), 1.31 (d, $J = 7.0$ Hz, 6H), 1.16 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 204.18, 163.84, 137.06, 127.52, 126.61, 81.99, 74.44, 52.09, 43.36, 31.39, 24.91, 24.59, 24.30, 24.10, 23.83; Anal. Calcd for C$_{15}$H$_{24}$O$_4$: C, 67.14; H, 9.01. Found: C, 67.17; H, 9.03.
Lippidulcine A (3a)

To a stirred solution of 15a (0.18 g, 0.56 mmol) in MeCN (0.5 mL) was added H₂O (60 mg, 3.36 mmol, 6 equiv) and TBAF (1 M, 1.1 mL, 1.12 mmol, 2 equiv) and the reaction was stirred for 30 min at rt. The reaction was diluted with CH₂Cl₂ (30 mL) and washed with brine (sat., 3 × 5 mL), dried over Na₂SO₄ and the solvent was removed under reduced pressure. Column chromatographic separation (eluent n-hexane/EtOAc in gradient: from n-hexane to 4:6) gave 3a as a yellowish solid (110 mg); 78% yield; Rᵣ=0.37 (1:9, n-hexane/EtOAc); [α]ᵣ= +132° (c 1.3, CHCl₃) vs. lit.⁶ [α]₀ = +123.6° (c 0.1, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 5.84 (dq, J = 2.1, 1.1 Hz, 1H), 5.79 (ddd, J = 15.8, 8.2, 5.9 Hz, 1H), 5.64 (dt, J = 15.7, 1.2 Hz, 1H), 5.21 (s, 1H), 2.36 (dd, J = 13.8, 4.6 Hz, 1H), 2.33 – 2.21 (m, 2H), 2.19 (dd, J = 5.9, 1.5 Hz, 1H), 2.16 (d, J = 8.1 Hz, 1H), 1.99 (ddd, J = 13.0, 4.5, 2.8 Hz, 1H), 1.95 – 1.89 (m, 3H), 1.63 (tdd, J = 13.3, 11.2, 5.8 Hz, 1H), 1.29 (s, 6H), 1.15 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 204.15, 163.51, 141.33, 127.60, 122.42, 74.37, 70.66, 52.01, 43.16, 31.39, 29.96, 28.99, 24.89, 24.09, 23.88; GC/MS: decomposes⁴ into two compounds tᵣ(3-methyl-2-cyclohexen-1-one) = 7.78 min; m/z (%) 110 (M⁺, 45), 54 (21), 39 (19), 82 (100), tᵣ(2° fragment)= 8.93 min; m/z (%) 124 (M⁺, 20), 109 (48), 43 (100); Anal. Calcd for C₁₅H₂₄O₃: C, 71.39; H, 9.59. Found: C, 71.35; H, 9.68.

Epilippidulcine A (3d).

To a stirred solution of lippidulcine A 3a (100 mg, 0.40 mmol) in MeCN (0.5 mL) was added HCl (1 M, 0.8 mL, 0.80 mmol, 2 equiv) and the reaction was stirred overnight at rt. The reaction was diluted with CH₂Cl₂ (30 mL) and washed with brine (sat., 3 × 5 mL), dried over Na₂SO₄ and the solvent was removed under reduced pressure.
Column chromatographic separation (eluent n-hexane/EtOAc in gradient: from n-hexane to 4:6) gave 3d as a colourless liquid (24 mg); 24% yield; Rf=0.30 (1:9 n-hexane/EtOAc); [α]D = -107° (c 1.2, CHCl3); 1H NMR (400 MHz, CDCl3) δ 5.83 (dq, J = 2.5, 1.1 Hz, 1H), 5.71 (ddd, J = 15.7, 7.6, 6.5 Hz, 1H), 5.59 (dt, J = 15.6, 1.1 Hz, 1H), 5.05 (s, 1H), 2.39 – 2.29 (m, 4H), 2.14 (ddd, J = 13.9, 7.6, 1.0 Hz, 1H), 2.06 (ddt, J = 13.0, 4.5, 2.8 Hz, 1H), 1.94 (t, J = 1.2 Hz, 3H), 1.87 (br s, 1H), 1.77 (dddd, J = 13.9, 13.0, 11.2, 5.5 Hz, 1H), 1.27 (d, J = 1.4 Hz, 6H), 1.16 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 203.34, 163.46, 141.15, 127.59, 122.98, 74.69, 70.68, 54.64, 40.91, 31.68, 29.80, 29.76, 26.16, 24.97, 24.11; GC/MS: decomposes into two compounds tr(3-methyl-2-cyclohexen-1-one) = 7.78 min; m/z (%) 110 (M+, 45), 54 (21), 39 (19), 82 (100), tr(2° fragment)= 8.93 min; m/z (%) 124 (M+, 20), 109 (48), 43 (100); Anal. Calcd for C15H24O3: C, 71.39; H, 9.59. Found: C, 71.42; H, 9.54.

(S)-6-((2S,5R)-5-Hydroxy-6-methyl-2-(trimethylsilyloxy)hept-6-en-2-yl)-3-methylcyclohex-2-enone (15b)

To a stirred solution of (S)-MeCBS (1 M, 0.85 mL, 0.85 mmol, 1.2 equiv) in CH2Cl2 (3 mL) was added BH$_3$·Me$_2$S (10.5 M, 74 μL, 0.78 mmol, 1.1 equiv) and the reaction was stirred at rt for 1 h. Then at −78 °C, a solution of 14 (0.23 g, 0.71 mmol) in CH2Cl2 (6 mL) was added over a 45 min period. The reaction was kept stirring for 17 h at −78 °C, then for 2 days at −60 °C. The reaction was quenched with slow addition of MeOH (1 mL) at −70 °C, then let stirred for 30 min at rt. Finally the reaction was diluted with CH2Cl2 (30 mL) and extracted with brine (sat., 3 × 5 mL), dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure. Column flash-chromatographic separation (eluent n-hexane/EtOAc, 8:2) gave 15b as a colorless-pale green liquid (184 mg); 80% yield; Rf=0.21 (7:3 n-hexane/EtOAc); tR = 25.36 min >99% purity by GC; [α]D = -1.6° (c 1.2, CHCl3); 1H NMR (400 MHz, CDCl3) δ 5.80 (h, J = 1.4 Hz, 1H), 4.93 (dq, J = 1.9, 0.9 Hz, 1H), 4.82 (ddt, J = 2.0, 1.5, 0.7 Hz, 1H), 4.03 (t, J = 5.7 Hz, 1H), 2.49 – 2.39 (m, 1H), 2.33 (dd, J = 8.8, 4.8 Hz, 1H), 2.21 (d, J
= 4.1 Hz, 1H), 2.20 – 2.12 (m, 2H), 2.05 – 1.94 (m, 1H), 1.90 (dd, J = 1.4, 0.8 Hz, 3H), 1.80 – 1.73 (m, 1H), 1.72 (ddt, J = 1.3, 0.9, 0.4 Hz, 3H), 1.65 – 1.58 (m, 2H), 1.44 (dd, J = 15.2, 5.6 Hz, 1H), 1.44 (s, 3H), 0.09 (s, 9H); 13C NMR (100 MHz, CDCl3) δ 200.17, 161.08, 147.54, 127.96, 110.77, 77.87, 75.78, 53.97, 35.20, 30.81, 30.04, 27.22, 24.02, 23.78, 17.53, 2.50; GC/MS: m/z (%) 309 (M+, 9), 225 (13), 105 (98), 75 (100); Anal. Calcd for C18H32O3Si: C, 66.62; H, 9.94. Found: C, 66.75; H, 9.81.

(S)-6-((2S,5S)-5-Hydroxy-6-methyl-2-(trimethylsilyloxy)hept-6-en-2-yl)-3-methylcyclohex-2-enone (15c)

The same procedure and work-up adopted for synthesis of 15b but with (R)-MeCBS. In this case the reaction was faster. Colourless liquid (207 mg); 82% yield; Rf=0.25 (7:3 n-hexane/EtOAc); tR = 25.31 min >99% purity by GC; [α]D = +3.5° (c 1.1, CHCl3); 1H NMR (400 MHz, CDCl3) δ 5.79 (q, J = 1.5 Hz, 1H), 4.94 (dt, J = 1.9, 1.0 Hz, 1H), 4.81 (ddq, J = 2.9, 1.4, 0.7 Hz, 1H), 4.01 (t, J = 5.9 Hz, 1H), 2.49 – 2.38 (m, 1H), 2.31 (dd, J = 9.0, 4.8 Hz, 1H), 2.23 – 2.11 (m, 3H), 2.05 – 1.93 (m, 1H), 1.90 (dt, J = 1.3, 0.7 Hz, 3H), 1.73 (ddd, J = 1.4, 0.9, 0.4 Hz, 3H), 1.71 – 1.63 (m, 2H), 1.59 – 1.47 (m, 2H), 1.44 (s, 3H), 0.08 (s, 9H); 13C NMR (100 MHz, CDCl3) δ 200.24, 161.13, 147.70, 128.15, 110.84, 78.02, 76.18, 54.26, 35.17, 31.01, 29.97, 27.51, 24.23, 23.94, 17.85, 2.64; GC/MS: m/z (%) 309 (M+, 8), 225 (20), 213 (5), 75 (100); Anal. Calcd for C18H32O3Si: C, 66.62; H, 9.94. Found: C, 66.54; H, 10.07.

Lippidulcine B (3b)
To a stirred solution of 15b (52.5 mg, 0.162 mmol) in MeCN (0.5 mL) was added H2O (18 mg, 0.97 mmol, 6 equiv) and TBAF (1 M, 320 μL, 0.32 mmol, 2 equiv) and the reaction was stirred for 30 min at rt. The reaction was diluted with CH2Cl2 (30 mL) and washed with brine (3 × 5 mL), dried over Na2SO4 and the solvent was removed under reduced pressure. Column flash chromatographic separation (elucent n-hexane/EtOAc 1:9) gave 3b as a colourless liquid 30 mg; 73% yield; Rf = 0.37 (1:9 n-hexane/EtOAc); [α]D = +123° (c 1.5, CHCl3) vs. lit.5 [α]D = +113.3° (c 0.4, CHCl3); 3b decomposes into the GC-MS4;1H NMR (400 MHz, CDCl3) δ 5.94 – 5.79 (m, 1H), 5.54 (s, 1H), 4.96 (dt, J = 6.0 Hz, 1H), 3.20 (s, 1H), 2.45 (dd, J = 14.0, 4.6 Hz, 1H), 2.41 – 2.33 (m, 1H), 2.28 (ddd, J = 18.5, 5.1, 2.6 Hz, 1H), 2.03 – 1.97 (m, 1H), 1.95 (td, J = 1.2, 0.6 Hz, 3H), 1.72 (ddd, J = 1.4, 0.9, 0.4 Hz, 3H), 1.71 – 1.49 (m, 5H), 1.18 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 204.02, 163.71, 147.83, 127.65, 110.52, 75.91, 74.23, 52.27, 36.53, 31.42, 29.20, 25.14, 24.15, 23.74, 18.28; Anal. Calcd for C15H24O3: C, 71.39; H, 9.59. Found: C, 71.29; H, 9.67.

**Lippidulcine C (3c)**

The same procedure and work-up adopted for synthesis of 3b. Colourless-yellowish liquid (33 mg); 79% yield; Rf = 0.37 (1:9, n-hexane/EtOAc); [α]D = +92.1° (c 1.7, CHCl3) vs. lit.5 [α]D = +119.8° (c 0.7, CHCl3); 3c decomposes into the GC-MS4;1H NMR (400 MHz, CDCl3) δ 5.86 (br s, 1H), 5.47 (s, 1H), 4.96 (ddt, J = 2.0, 1.0, 0.4 Hz, 1H), 4.82 (ddd, J = 2.1, 1.5, 0.6 Hz, 1H), 4.03 (t, J = 5.6 Hz, 1H), 2.88 (s, 1H), 2.41 (dd, J = 14.0, 4.8 Hz, 1H), 2.36 (br d, J = 12.2 Hz, 1H), 2.28 (ddd, J = 18.6, 5.0, 2.3 Hz, 1H), 2.02 (ddt, J = 15.7, 4.6, 2.6 Hz, 1H), 1.95 (dq, J = 1.4, 0.5 Hz, 3H), 1.83 – 1.73 (m, 1H), 1.72 (ddd, J = 1.4, 0.9, 0.5 Hz, 3H), 1.69 – 1.51 (m, 4H), 1.17 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 204.03, 163.73, 147.93, 127.64, 110.57, 75.75, 74.14, 52.25, 36.16, 31.43, 28.82, 25.13, 24.15, 23.81, 18.28; Anal. Calcd for C15H24O3: C, 71.39; H, 9.59. Found: C, 71.43; H, 9.65.
3. Sensorial evaluation criteria
A panel of four persons of different age, tasted a sample of 3 mg of each substance.

4. Notes and references
4. The high temperature of GC-injector induces the spontaneous retro aldolic reaction.
5. Copies of $^1H$ and $^{13}C$ NMR spectra

(S)-isopulegone - $^1H$ - CDCl$_3$ - 400MHz

![NMR Spectrum of (S)-isopulegone - $^1H$](image)

C$_{10}$H$_{16}$O

(S)-isopulegone - $^{13}C$ - CDCl$_3$ - 100MHz

![NMR Spectrum of (S)-isopulegone - $^{13}C$](image)

C$_{10}$H$_{16}$O
ester - $^1$H - CDCl$_3$ - 400MHz

ester - $^{13}$C - CDCl$_3$ - 125MHz

$C_{17}H_{21}NO_4$

$C_{17}H_{21}NO_4$
4 - (+)-Neoisopulegol - $^1$H - CDCl$_3$ - 400MHz

$\text{C}_{10}\text{H}_{18}\text{O}$

4 - (+)-Neoisopulegol - $^{13}$C - CDCl$_3$ - 100MHz

$\text{C}_{10}\text{H}_{18}\text{O}$
5 - alkyl derivative - $^1$H - CDCl$_3$ - 400MHz

5 - alkyl derivative - $^{13}$C - CDCl$_3$ - 100MHz
6 - epoxide - $^1$H - CDCl$_3$ - 400MHz

\[ \text{C}_{15}\text{H}_{26}\text{O}_2 \]

6 - epoxide - $^{13}$C - CDCl$_3$ - 125MHz

\[ \text{C}_{15}\text{H}_{26}\text{O}_2 \]
7 - diol-^1^H - CDCl₃ - 400MHz

C₁₆H₂₈O₂

7 - diol-^1^C - CDCl₃ - 100MHz

C₁₅H₂₈O₂
8 - ketone - $^1$H - CDCl$_3$ - 400MHz

$^1$I

C$_{15}$H$_{26}$O$_2$

8 - ketone - $^{13}$C - CDCl$_3$ - 100MHz

$^1$I

C$_{15}$H$_{26}$O$_2$
9 - trimethyl silyl ether derivative - $^1$H - CDCl$_3$ - 400MHz

C$_{18}$H$_{34}$O$_2$Si

9 - trimethyl silyl ether derivative - $^{13}$C - CDCl$_3$ - 100MHz

C$_{18}$H$_{34}$O$_2$Si
10a - triethyl silyl enol ether - $^1$H - CDCl$_3$ - 400MHz

\[ \text{C}_{24}\text{H}_{48}\text{O}_2\text{Si}_2 \]

10a - triethyl silyl enol ether - $^{13}$C - CDCl$_3$ - 100MHz

\[ \text{C}_{24}\text{H}_{48}\text{O}_2\text{Si}_2 \]
11 - silyl hernandulcin - $^1$H - CDCl$_3$ - 400MHz

$$\text{C}_{18}\text{H}_{32}\text{O}_2\text{Si}$$

11 - silyl hernandulcin - $^{13}$C - CDCl$_3$ - 100MHz
2 - hydroperoxide mixture - $^1$H - CDCl$_3$ - 400MHz

2a
$C_{15}H_{24}O_4$

2b: (5'R)-hydroperoxy

2c: (5'S)-hydroperoxy

2 - hydroperoxide mixture - $^{13}$C - CDCl$_3$ - 100MHz

2a
$C_{15}H_{24}O_4$

2b: (5'R)-hydroperoxy

2c: (5'S)-hydroperoxy
12 - TBDPsilyl-peroxylippidulcine A - $^1$H - CDCl$_3$ - 400MHz

C$_{31}$H$_{42}$O$_4$Si

12 - TBDPsilyl-peroxylippidulcine A - $^{13}$C
CDCl$_3$ - 100MHz

C$_{31}$H$_{42}$O$_4$Si
2a - peroxyllipidulcine A - $^1$H - CDCl$_3$ - 400MHz

\[
\begin{align*}
\text{C}_ {15}\text{H}_ {24}\text{O}_4
\end{align*}
\]

2a - peroxyllipidulcine A - $^{13}$C - CDCl$_3$ - 100MHz

\[
\begin{align*}
\text{C}_ {15}\text{H}_ {24}\text{O}_4
\end{align*}
\]
15a - lippidulcine A-OTMS - $^1$H - CDCl$_3$ - 400 MHz

C$_{18}$H$_{32}$O$_3$Si

15a - lippidulcine A-OTMS - $^{13}$C - CDCl$_3$ - 100 MHz

C$_{18}$H$_{32}$O$_3$Si
3a - lippidulcine A - $^1$H - CDCl$_3$ - 400 MHz

C$_{15}$H$_{24}$O$_3$

3a - lippidulcine A - $^{13}$C - CDCl$_3$ - 100 MHz

C$_{15}$H$_{24}$O$_3$
3d - epiippidulcine A - $^1$H - CDCl$_3$ - 400 MHz

C$_{15}$H$_{24}$O$_3$

3d - epiippidulcine A - $^{13}$C - CDCl$_3$ - 100 MHz

C$_{15}$H$_{24}$O$_3$
14 - ketone-Il-OTMS - $^1$H - CDCl$_3$ - 400 MHz

C$_{18}$H$_{30}$O$_3$Si

14 - ketone-Il-OTMS - $^{13}$C - CDCl$_3$ - 100 MHz

C$_{18}$H$_{30}$O$_3$Si
15b - lippidulcine B-OTMS - $^1$H - CDCl$_3$ - 400 MHz

C$_{18}$H$_{32}$O$_3$Si

15b - lippidulcine B-OTMS - $^{13}$C - CDCl$_3$ - 100 MHz

C$_{18}$H$_{32}$O$_3$Si
3b - lippidulcine B - \(^1\)H - CDCl\(_3\) - 400 MHz

C\(_{15}\)H\(_{24}\)O\(_3\)

3b - lippidulcine B - \(^{13}\)C - CDCl\(_3\) - 100 MHz

C\(_{15}\)H\(_{24}\)O\(_3\)
15c - lippidulcine C-OTMS - $^1$H - CDCl$_3$ - 400 MHz

C$_{18}$H$_{32}$O$_3$Si

15c - lippidulcine C-OTMS - $^{13}$C
CDCl$_3$ - 100 MHz

C$_{18}$H$_{32}$O$_3$Si
$3c$ - lippidulcine C - $^1H$ - CDCl$_3$ - 400 MHz

$C_{15}H_{24}O_3$

$3c$ - lippidulcine C - $^{13}C$ - CDCl$_3$ - 100 MHz

$C_{15}H_{24}O_3$