Supporting Information
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Supporting Information

Total Synthesis of (+)-Mintlactone and (-)-Isomintlactone via SmI$_2$-Induced Radical Cyclization

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General information-

NMR spectra were recorded on Bruker 400 MHz (400 MHz for $^1$H NMR and 100 MHz for $^{13}$C NMR) spectrometers. Proton chemical shifts are reported relative to residual solvent peak (CDCl$_3$ at 7.26 ppm). Carbon chemical shifts are reported in ppm, and coupling constants ($J$) are in Hertz (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br = broad. High-resolution mass spectra (HRMS) were measured on a Brucker Daltonics Apex II 47e Specification (for HRMS). Substrates were purchased from commercial sources and used as received. Reactions were carried out in dry solvents under argon atmosphere unless otherwise noted.

Experimental procedure

*(S)-tert-Butyl((3,7-dimethyloct-6-en-1-yl)oxy)dimethylsilane (3)*

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\text{OTBS}
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To a solution of imidazole (2.4 g, 35 mmol) and TBSCI (5.3 g, 35 mmol) in 6 ml DMF was added citronellol (5.0 g, 32 mmol) and the mixture was stirred for 15 min at room temperature. Then the reaction was quenched by addition of H$_2$O (100 mL) and the mixture was extracted with EtOAc (3 × 20 mL). The solvents were evaporated under reduced pressure and purified by flash column chromatography to afford 3 (8.4 g, 97%) as a colorless oil.

*(S)-6-((tert-Butyldimethylsilyl)oxy)-4-methylhexanal (4)*

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\text{OTBS}
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To a solution of substrate 3 (3.0 g, 11 mmol) in EtOAc/CH$_3$CN/H$_2$O (3:3:1, 140 mL) at 0 °C was added RuCl$_3$ (0.16 g, 0.77 mmol) and the mixture was stirred for 1 min. To the solution was added NaIO$_4$ (3.6 g, 17 mmol) and the mixture was stirred violently for 3 min. Then the mixture was warmed to room temperature and quenched by addition of aqueous Na$_2$S$_2$O$_3$ (5 mL). The organic layer was separated and extracted with EtOAc (3 × 20 mL). The solvents were evaporated under reduced pressure and purified by flash column chromatography to give the crude diol. To a solution of the crude diol obtained above in 20 mL of CH$_3$CN and 20 mL of H$_2$O was
added NaIO₄ (1.6 g, 7.5 mmol). After stirring for 4 h at room temperature, the reaction was quenched with aqueous Na₂S₂O₃ (5 mL), extracted with EtOAc (3 × 20 mL), concentrated, and chromatographed. And 1.6 g (59%) of compounds 4 was provided as a colorless oil.

(S,E)-Methyl 8-((tert-butyldimethylsilyl)oxy)-2,6-dimethyloct-2-enoate (6)

A solution of substrate 5 (2.3 g, 6.6 mmol) and 4 (1.3 g, 5.3 mmol) in 25 ml CH₂Cl₂ was stirred for 2 h at room temperature. Then the solvents were removed under reduced pressure and the crude product was purified by flash column chromatography to afford 6 (pure compound 1.6 g, 96%) as a light yellow liquid.

¹H NMR (400 MHz, CDCl₃) δ 6.77 (td, J = 7.4, 1.2 Hz, 1H), 3.74 (s, 3H), 3.65 (dd, J = 14.5, 6.9 Hz, 2H), 2.25 - 2.14 (m, 2H), 1.85 (s, 3H), 1.66 - 1.53 (m, 2H), 1.34 (ddd, J = 22.9, 19.2, 15.3 Hz, 3H), 0.94 - 0.87 (m, 12H), 0.06 (s, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 168.7, 142.7, 127.3, 61.2, 51.6, 39.7, 35.8, 29.2, 26.2, 25.9, 19.5, 18.3, 12.3, -5.3.


(S,E)-Methyl 2,6-dimethyl-8-oxooct-2-enoate (7)

To a solution of substrate 6 (1.3 g, 4.1 mmol) in THF (20 mL) at 0 °C was added TBAF (6.0 mL of a 1.0 mol/L solution in THF). After stirring for 3 min, the solution was warmed to room temperature and stirred for another 1 h. The reaction was diluted with H₂O, then the organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The solvents were evaporated under reduced pressure and the product was dissolved in CH₂Cl₂. Then 5A molecular sieve (3.2 g) was added. After stirring for 1 min, to the reaction mixture was added PCC (1.6 g, 7.4 mmol). After stirring for 3 min at room temperature, the reaction mixture was purified by flash column chromatography on silica gel to afford 7 (0.76 g, 93%) as a light yellow liquid.

¹H NMR (400 MHz, CDCl₃) δ 9.75 (s, 1H), 6.72 (t, J = 7.3 Hz, 1H), 3.73 (s, 3H), 2.42 (dd, J = 16.2, 5.6 Hz, 1H), 2.32 - 2.25 (m, 1H), 2.18 (dd, J = 14.5, 7.1 Hz, 2H), 2.09 (dd, J = 13.4, 6.8 Hz, 1H), 1.83 (s, 3H), 1.50 - 1.35 (m, 2H), 0.98 (d, J = 6.6 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 202.3, 168.5, 141.7, 127.8, 51.7, 50.8, 35.5, 27.7, 26.0, 19.6, 12.3.


(3aR,6S,7aS)-3,6-Dimethylhexahydrobenzofuran-2(3H)-one (8)
To the freshly made Sm powder (0.24 g, 1.6 mmol) was added THF (4.0 mL) and CH₂I₂ (0.40 g, 1.5 mmol) at the room temperature and the mixture was stirred for 40 min (the color of the solution turns to dark blue). Then to the solution was added t-BuOH (0.15 g, 2.0 mmol) at -20 °C. After stirring for 5 min, substrate 7 (0.1 g, 0.5 mmol) in anhydrous THF (1.0 mL) was dropwise added. After stirring for 2 h, saturated NH₄Cl was added to quench the reaction. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The solvents were evaporated under reduced pressure and the crude product was purified by flash column chromatography to yield 8 (57 mg, 68%) as a yellow oil.

(S,Z)-Methyl 8-((tert-butyldimethylsilyl)oxy)-2,6-dimethyloct-2-enoate (10)

To a solution of substrate 9 (0.96 g, 4.9 mmol) in THF (20 mL) at -78 °C was added 60% NaH (0.33 g, 8.3 mmol). After stirring for 15 min, a solution of substrate 4 (1.0 g, 4.1 mmol) in 20 mL of THF was added. After stirring for another 6 h, the reaction was quenched with saturated NH₄Cl (10 mL) and the mixture was extracted with EtOAc (3 × 20 mL). The solvents were removed under reduced pressure and purified by flash column chromatography to afford 10 (pure compound 1.05 g, 82%) as a light yellow liquid.

1H NMR (400 MHz, CDCl₃) δ 5.91 (td, J = 7.4, 1.2 Hz, 1H), 3.72 (s, 3H), 3.68 - 3.57 (m, 2H), 2.51 - 2.38 (m, 2H), 1.87 (d, J = 1.2 Hz, 3H), 1.55 (tt, J = 12.4, 6.1 Hz, 2H), 1.31 (dddd, J = 14.7, 13.2, 6.5, 4.3 Hz, 3H), 0.88 (d, J = 4.5 Hz, 12H), 0.03 (s, 6H).

13C NMR (101 MHz, CDCl₃) δ 168.5, 143.6, 126.7, 61.3, 51.1, 39.8, 36.7, 32.7, 29.2, 27.1, 25.9, 20.6, 19.5, 18.3, -5.3.


(S,Z)-Methyl 2,6-dimethyl-8-oxooct-2-enoate (11)

The title compound was synthesized according to the procedures employed by the preparation of 7 to give product 11 (91%) as a light yellow oil.

1H NMR (400 MHz, CDCl₃) δ 9.76 (s, 1H), 5.92 (td, J = 7.5, 1.4 Hz, 1H), 3.74 (s, 3H), 2.49 (d, J = 1.1 Hz, 1H), 2.44 (ddd, J = 16.3, 5.6, 1.7 Hz, 2H), 2.25 (ddd, J = 16.2, 7.9, 2.5 Hz, 1H), 2.09 (dd, J = 13.4, 6.8 Hz, 1H), 1.90 (d, J = 1.3 Hz, 3H), 1.33 - 1.48 (m, 2H), 0.99 (d, J = 6.7 Hz, 3H).

13C NMR (101 MHz, CDCl₃) δ 202.6, 168.3, 142.7, 127.2, 51.2, 50.8, 36.3, 27.8, 26.9,
(3aR,6S,7aR)-3,6-Dimethylhexahydrobenzofuran-2(3H)-one (12)

The title compound was synthesized according to the procedures employed by the preparation of 8 to give product 12 (67%) as a light yellow oil.

(+)-Mintlactone (1)

To a solution of substrate 8 (100 mg, 0.59 mmol) in 2 mL anhydrous THF, 0.90 mL of KHMDS (1 mmol/L in THF) was added at -78 °C. After stirring for 20 min, chlorotrimethylsilane (83 mg, 0.76 mmol) was added. To the resultant solution, NBS (139 mg, 0.78 mmol) in 2 mL THF was added after a further 15 minutes. The reaction mixture was stirred at -78 °C for 4 h. And then 1 mL saturated NH₄Cl was added to quench the reaction. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The solvents were evaporated under reduced pressure and the crude bromolactone. To a solution of the crude bromolactone obtained above in 4 mL toluene, DBU (91 mg, 0.60 mmol) was added. The reaction mixture was refluxed for 90 min, and solvent was removed under reduced pressure to furnish a residue. Then the residue was purified with column chromatography to afford 1 (mixture of isomers 67 mg, 68%) as a colorless oil. \([\alpha]^{17}_{D} = +52.6 \ (c = 1.0, \text{CHCl}_3)\).

\(^1\)H NMR (400 MHz, CDCl₃) δ 4.60 (dd, \(J = 11.3, 6.1 \text{ Hz}, 1\text{H})\), 2.77 (ddd, \(J = 14.2, 4.3, 1.8 \text{ Hz}, 1\text{H})\), 2.45 - 2.36 (m, 1H), 2.17 (td, \(J = 13.8, 5.6 \text{ Hz}, 1\text{H})\), 1.99 - 1.88 (m, 1H), 1.79 (t, \(J = 1.5 \text{ Hz}, 3\text{H})\), 1.75 - 1.64 (m, 1H), 1.06 - 0.93 (m, 5H).

\(^13\)C NMR (101 MHz, CDCl₃) δ 174.8, 162.3, 119.6, 79.9, 42.0, 34.6, 29.8, 25.5, 21.2, 8.2.


(-)-Isomintlactone (2)

To a solution of substrate 8 (90 mg, 0.54 mmol) in 2mL anhydrous THF, 0.64 mL of KHMDS (1.0 mmol/L in THF) was added at -78 °C. After stirring for 20 min, PhSeCl (134 mg, 0.70 mmol) in 2 mL THF was added. The reaction mixture was stirred at -78 °C for 4 h. And then 1 mL saturated NH₄Cl was added to quench the reaction. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The solvents were evaporated under reduced pressure to give crude
selenolactone. To the crude product dissolved in 4 mL THF, 0.1 ml of 30% H₂O₂ was added at 0 °C. After stirring for 3min, the reaction was allowed to be warmed to room temperature to stir another 3min. And then the reaction was quenched with aqueous Na₂S₂O₃ and extracted with EtOAc (3 × 5 mL). The solvents were evaporated under reduced pressure and the crude product was purified by flash column chromatography to yield 2 (mixture of isomers 45 mg, 51%) as a light yellow oil. [α]¹⁷D = -72.8 (c = 1.0, CHCl₃).

¹H NMR (400 MHz, CDCl₃) δ 4.77 (dd, J = 11.0, 6.2 Hz, 1H), 2.66 (ddd, J = 14.3, 4.6, 1.7 Hz, 1H), 2.42 - 2.23 (m, 3H), 1.79 - 1.77 (m, 4H), 1.58 - 1.46 (m, 1H), 1.33 (td, J = 12.0, 4.6 Hz, 1H), 1.12 (d, J = 7.4 Hz, 3H).
¹³C NMR (101 MHz, CDCl₃) δ 174.9, 163.0, 119.3, 77.4, 39.6, 31.7, 27.3, 21.8, 17.2, 8.1.

The image contains a chemical structure labeled as '6' with various functional groups including methyl groups, a vinyl group, and an oxygen atom. The structure is accompanied by a 1H NMR spectrum with chemical shifts indicated on the x-axis in parts per million (ppm). The spectrum shows multiple peaks at various ppm values, suggesting the presence of different chemical environments in the molecule.
1
2