

First Total Synthesis of Paracaseolide A

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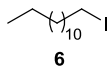
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Part A: Experimental Procedures

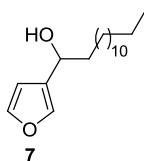
Preparation of iodide **6**



To a solution of the alcohol **5** (2.0 g, 10 mmol) in dry CH₂Cl₂ (50 mL) at room temperature, imidazole (1.36 g, 20 mmol), PPh₃ (5.24 g, 20 mmol) and I₂ (5.0 g, 19.7 mmol) were added. The reaction mixture was stirred for 30 minutes at room temperature and then Na₂S₂O₃ (sat. aq. 30 mL) was added. The layers were separated and the organic solution was concentrated to half its previous volume and then diluted with petroleum ether (30 mL). The Ph₃P=O that had precipitated, was removed by filtration and the remaining solution was concentrated in *vacuo* and purified by column chromatography (silica gel, petroleum ether:EtOAc = 1:0 → 40:1) to afford the iodide **6** (3.04 g, 98%).

6: ¹H NMR (300 MHz, CDCl₃): δ = 3.18 (t, *J* = 7.1 Hz, 2H), 1.82 (m, 2H), 1.38 (m, 2H), 1.26 (brs, 18H), 0.88 (t, *J* = 6.6 Hz, 3H) ppm; ¹³C NMR (75 MHz, CDCl₃): δ = 33.6, 31.9, 30.5, 29.7, 29.6 (2C), 29.5, 29.4, 29.3, 28.5, 22.7, 14.1, 7.2 ppm.

Synthesis of furanol **7**

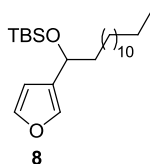


To a solution of iodide **6** (3.0 g, 9.7 mmol) in anhydrous Et₂O (80 mL) at −78 °C, a solution of *t*-BuLi (12.1 mL of 1.7 M in pentane, 20.6 mmol) was added dropwise. The cooling bath was removed 15 minutes after completion of the addition of *t*-BuLi, and the reaction mixture was allowed stirred at room temperature for 45 minutes. The reaction mixture was recooled to −78 °C and a solution of 3-furaldehyde (535 μL, 6.4 mmol) in anhydrous Et₂O (10 mL) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 90 minutes and then Et₂O (10 mL) and NH₄Cl (sat. aq. 50

mL) were added. The layers were separated and the organic layer was dried with Na₂SO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 40:1 → 10:1) to afford alcohol **7** (2.61 g, 96%).

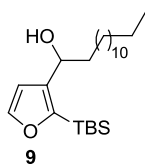
7: ¹H NMR (300 MHz, CDCl₃): δ = 7.37 (m, 2H), 6.39 (d, *J* = 1.0 Hz, 1H), 4.62 (t, *J* = 6.6 Hz, 1H), 1.91 (brs, -OH) 1.71 (m, 2H), 1.25 (brs, 22H), 0.88 (t, *J* = 6.7 Hz, 3H) ppm; ¹³C NMR (75 MHz, CDCl₃): δ = 143.2, 138.9, 129.3, 108.4, 67.0, 37.8, 31.9, 29.7, 29.6 (4C), 29.5, 29.4, 29.3, 25.6, 22.7, 14.1 ppm. HRMS (TOF ESI): calcd for C₁₈H₃₂NaO₂: 303.2295 [M + Na]⁺; found: 303.2287.

Silylation of furanol **7**



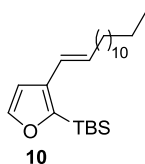
To a solution of the alcohol **7** (1.8 g, 6.4 mmol) in anhydrous DMF (18 mL) at room temperature, imidazole (1.1 g, 16.2 mmol), TBSCl (1.4 g, 9.3 mmol) and 4-DMAP (38 mg, 0.31 mmol) were added. After the reaction solution had been stirred for 12 hours at this temperature, it was quenched with MeOH (0.5 mL). The stirring was continued for a further 1 hour, after which time the mixture was partitioned between Et₂O (40 mL) and H₂O (3 × 10 mL). The organic extract was dried with Na₂SO₄ and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 40:1 → 10:1) to afford the TBS-protected furanol **8** (2.12 g, 84%).

8: ¹H NMR (300 MHz, CDCl₃): δ = 7.34 (t, *J* = 1.6 Hz, 1H), 7.28 (d, *J* = 0.7 Hz, 1H), 6.34 (m, 1H), 4.64 (t, *J* = 6.3 Hz, 1H), 1.62 (m, 2H), 1.26 (brs, 22H), 0.88 (m, 9H of *t*-Bu plus 3H of Me), 0.05 (s, 3H), -0.05 (s, 3H) ppm; ¹³C NMR (75 MHz, CDCl₃): δ = 142.7, 138.6, 130.1, 108.8, 67.7, 39.6, 31.9, 29.7 (4C), 29.6 (2C), 29.5, 29.4, 25.8 (3C), 25.3, 22.7, 18.2, 14.1, -4.7, -4.9 ppm. HRMS (TOF ESI): calcd for C₂₄H₄₆NaO₂Si: 417.3159 [M + Na]⁺; found: 417.3152.

[1,4] O→C silyl migration

To a stirred solution of TBS-protected furanol **8** (2.0 g, 5.06 mmol) in anhydrous THF (80 mL) at room temperature was added dry HMPA (1.0 mL, 6.07 mmol). The solution was cooled to 0 °C and *n*-BuLi (1.6 M in hexane, 5.7 mL, 9.12 mmol) added dropwise. The reaction mixture was warmed to room temperature and stirred for 30 minutes and then Et₂O (30 mL) and NH₄Cl (sat. aq. 40 mL) were added. The layers were separated and the organic layer was dried with Na₂SO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 10:1) to afford furylic alcohol **9** (1.92 g, 96%).

9: ¹H NMR (300 MHz, CDCl₃): δ = 7.57 (d, *J* = 1.7 Hz, 1H), 6.47 (d, *J* = 1.7 Hz, 1H), 4.73 (t, *J* = 6.6 Hz, 1H), 1.82 (m, 1H), 1.66 (m, 1H plus 1-OH), 1.26 (brs, 22H), 0.92 (s, 9H), 0.88 (t, *J* = 6.6 Hz, 3H), 0.30 (s, 3H), 0.28 (s, 3H) ppm; ¹³C NMR (75 MHz, CDCl₃): δ = 154.2, 146.8, 140.0, 107.7, 66.6, 38.2, 31.9, 29.7 (2C), 29.6 (3C), 29.5(2C), 29.3, 26.4 (3C), 26.1, 22.7, 17.2, 14.1, -5.2, -5.5 ppm. HRMS (TOF ESI): calcd for C₂₄H₄₆NaO₂Si: 417.3159 [M + Na]⁺; found: 417.3164.

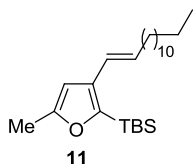
Dehydration of furanol 9

A solution of furylic alcohol **9** (1.9 g, 4.81 mmol), with a catalytic amount of *p*-TsOH (0.05 equiv, 46 mg) and molecular sieves 4Å in toluene (80 mL) was heated in a sealed tube at 140 °C (oil bath temperature) for 12 hours. The reaction mixture was left to cool to room temperature, NaHCO₃ (sat. aq. 30 mL) and Et₂O (25 mL) were added. The layers were separated and the organic layer was dried with Na₂SO₄ and concentrated *in vacuo*.

The residue was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 50:1) to afford olefin **10** (1.41 g, 78%).

10: ^1H NMR (300 MHz, CDCl_3): δ = 7.55 (dd, J_1 = 1.7 Hz, J_2 = 0.7 Hz, 1H), 6.57 (d, J = 1.7 Hz, 1H), 6.43 (d, J = 15.6 Hz, 1H), 5.98 (dt, J_1 = 15.6 Hz, J_2 = 6.9 Hz, 1H), 2.21 (m, 2H), 1.50 (m, 2H), 1.32 (brs, 18H), 0.96 (s, 9H), 0.94 (t, J = 6.9 Hz, 3H) 0.35 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3): δ = 154.5, 146.4, 135.3, 130.8, 121.1, 107.4, 33.0, 32.0, 29.8 (2C), 29.7 (2C), 29.6, 29.4 (2C), 29.2, 26.4 (3C), 22.7, 17.7, 14.1, -5.6 (2C) ppm. HRMS (TOF ESI): calcd for $\text{C}_{24}\text{H}_{45}\text{OSi}$: 377.3234 $[\text{M} + \text{H}]^+$; found: 377.3235.

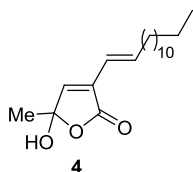
Ortho-methylation of furan **10**



To a solution of furan **10** (950 mg, 2.52 mmol) in anhydrous THF (20 mL), at 0 °C, *n*-BuLi (3.2 mL of 1.6 M solution in hexane, 5.04 mmol) was added dropwise. After 30 min stirring at the same temperature, a solution of CH_3I (471 μL , 7.56 mmol) in anhydrous THF (5 mL) was added dropwise. The reaction mixture was warmed to room temperature and stirred for a further 2 h after which it was partitioned between Et_2O (20 mL) and NH_4Cl (sat. aq. 20 mL). The layers were separated and the organic layer was dried with Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 50:1) to afford trisubstituted furan **11** (827 mg, 84%).

11: ^1H NMR (300 MHz, CDCl_3): δ = 6.33 (d, J = 15.6 Hz, 1H), 6.14 (s, 1H), 5.87 (dt, J_1 = 15.6 Hz, J_2 = 6.9 Hz, 1H), 2.28 (s, 3H), 2.14 (q, J = 6.7 Hz, 2H) 1.43 (m, 2H), 1.28 (brs, 18H), 0.92 (s, 9H), 0.90 (t, J = 6.9 Hz, 3H), 0.29 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3): δ = 156.3, 152.8, 136.4, 130.3, 121.4, 103.7, 33.0, 31.9, 29.7 (4C), 29.5, 29.4 (2C), 29.1, 26.5 (3C), 22.7, 17.6, 14.1, 13.7, -5.4 (2C) ppm. HRMS (TOF ESI): calcd for $\text{C}_{25}\text{H}_{47}\text{OSi}$: 391.3391 $[\text{M} + \text{H}]^+$; found: 391.3388.

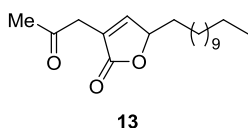
Photooxygenation of furan **11**



A solution of the furan **11** (300 mg, 0.77 mmol) in CH₂Cl₂ (25 mL) containing methylene blue (10⁻⁴ M) was placed in a long vial and oxygen was bubbled gently through it. The solution was cooled to 0 °C and irradiated with xenon Variac Eimac Cermac 300 W visible light lamp for 5 min after which time complete consumption of the starting material was observed (based on tlc). SiO₂ and a few drops of H₂O were added, and the mixture was stirred vigorously for 1 h. After the filtration the solvent was removed *in vacuo*, and the residue was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 20:1 → 5:1) to afford 4-hydroxybutenolide **4** (124 mg, 52%).

4: ¹H NMR (300 MHz, CDCl₃): δ = 6.82 (s, 1H), 6.75 (dt, *J*₁ = 15.9 Hz, *J*₂ = 7.0 Hz, 1H), 6.02 (d, *J* = 15.9 Hz, 1H), 4.23 (brs, 1-OH), 2.14 (q, *J* = 7.0 Hz, 2H), 1.68 (s, 3H), 1.41 (m, 2H), 1.24 (brs, 18H), 0.86 (t, *J* = 6.6 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 170.3, 144.1, 140.9, 130.7, 117.8, 104.1, 33.5, 31.9, 29.7 (2C), 29.6 (2C), 29.5, 29.3, 29.2, 28.6, 24.8, 22.7, 14.1 ppm. HRMS (TOF ESI): calcd for C₁₉H₃₂NaO₃: 331.2244 [M + Na]⁺; found: 331.2236.

Formation of α,γ-disubstituted butenolide **13**

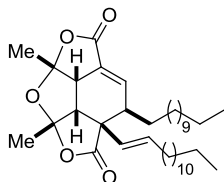


A solution of hydroxybutenolide **4** (63 mg, 0.20 mmol), in toluene (1 mL) was heated in a sealed tube at 110 °C for 12 hours. The reaction mixture was left to cool to room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 10:1→2:1) to afford disubstituted butenolide **13** (26 mg, 42%).

13: ¹H NMR (300 MHz, CDCl₃): δ = 7.37 (d, *J* = 1.5 Hz, 1H), 4.98 (m, 1H), 3.44 (s, 2H), 2.25 (s, 3H), 1.70 (m, 2H), 1.24 (brs, 20H), 0.87 (t, *J* = 6.7 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 203.1, 173.4, 152.2, 126.5, 82.0, 38.8, 33.3, 31.9, 30.2, 29.6(3C), 29.5,

29.3(3C), 25.0, 22.6, 14.1 ppm. HRMS (TOF ESI): calcd for $C_{19}H_{32}NaO_3$: 331.2244 [$M + Na$] $^+$; found: 331.2237.

[4+2]-Dimerization/ketalization/epimerization of the 4-hydroxybutenolide **4 to paracaseolide A (**1**)**



1: Paracaseolide A

A solution of 4-hydroxybutenolide **4** (71 mg, 0.23 mmol) was heated neat in a sealed tube at 110 °C for 12 hours. The reaction was left to cool to room temperature. The crude 1H -NMR revealed the formation of a mixture of paracaseolide A (**1**) and the byproduct butenolide **13** in 3:1 ratio. The mixture was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 20:1→5:1) to afford paracaseolide A **1** as an amorphous white powder (41 mg, 59%).

1: 1H NMR (300 MHz, $CDCl_3$): δ = 7.25 (dd, J_1 = 7.5 Hz, J_2 = 3.1 Hz, 1H), 5.83 (dt, J_1 = 15.7 Hz, J_2 = 6.9 Hz, 1H), 5.48 (d, J = 15.7 Hz, 1H), 3.37 (dd, J_1 = 9.5 Hz, J_2 = 3.1 Hz, 1H), 3.30 (d, J = 9.5 Hz, 1H), 3.04 (m, 1H), 2.11 (m, 2H), 1.76 (s, 3H), 1.67 (m, 1H), 1.62 (s, 3H), 1.25 (brs, 41H), 0.88 (t, J = 6.7 Hz, 6H) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.0, 166.1, 144.7, 135.1, 129.3, 126.3, 115.3, 113.8, 58.3, 50.3, 46.7, 45.1, 32.7, 31.9 (2C), 29.6 (8C), 29.5, 29.4 (2C), 29.3 (2C), 29.1, 29.0, 28.2, 28.0, 26.6, 25.7, 22.7 (2C), 14.1 (2C) ppm. HRMS (TOF ESI): calcd for $C_{38}H_{63}O_5$: 599.4670 [$M + H$] $^+$; found: 599.4669.

Part B: Copies of ^1H - and ^{13}C -NMR spectra



(6, 300 MHz, CDCl₃)

