D-2-hydroxyglutarate synthesis

To a suspension of (R)-2-amino-5-(benzyloxy)-5-oxopentanoic acid (1.430 g, 6.027 mmol, Merck) in H₂O (48 mL) and AcOH (12 mL) was added a freshly prepared aqueous solution of NaNO₂ (12 mL, 1.0 M, 12 mmol) dropwise at 0°C with stirring. After the addition was complete, the reaction mixture was allowed to warm to RT, wherein the reaction mixture clarified. After stirring for 18 h, the solvent was removed on a rotary evaporator (50 mBar, 48°C water bath) and the resulting solid was dried under high vacuum to give (R)-5-(benzyloxy)-2-hydroxy-5-oxopentanoic acid as a white solid. To a solution of this dried crude product in anhydrous DMF (12 mL) was added NaHCO₃ (507 mg, 6.03 mmol) followed by octyl iodide (2.20 mL, 12.1 mmol, Sigma) at RT under argon. The reaction vessel was wrapped in foil and stirred in the dark. After 18 h, the reaction mixture was diluted with H₂O (200 mL) and EtOAc (50 mL). The two layers were separated and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried (MgSO₄), filtered, concentrated, and purified by column chromatography (0–30% gradient of EtOAc in petroleum ether) to give 631 mg (60%, 2 steps) of (R)-5-benzyl 1-octyl 2-hydroxypentanedioate as a colorless oil:

Rₛ 0.34 (20% EtOAc in petroleum ether)

¹H NMR (400 MHz, CDCl₃): δ 7.39–7.29 (m, 5 H), 5.13 (s, 2 H), 4.22 (ddd, J = 8.0, 5.4, 4.2 Hz, 1 H), 4.17 (t, J = 6.8 Hz, 2 H), 2.84 (d, J = 5.4 Hz, 1 H), 2.57 (ddd, J = 16.5, 8.4, 7.0 Hz, 1 H), 2.49 (ddd, J = 16.5, 8.4, 6.0 Hz, 1 H), 2.20 (ddddd, J = 14.1, 8.5, 7.1, 4.2 Hz, 1 H), 1.95 (dddd, J = 14.2, 8.2, 8.2, 6.1 Hz, 1 H), 1.70–1.61 (m, 2 H), 1.38–1.21 (m, 10 H), 0.88 (t, J = 6.8 Hz, 3 H) ppm (supplement figure 2).

To a solution of (R)-5-benzyl 1-octyl 2-hydroxypentanedioate (1.259 g, 3.593 mmol) in EtOAc (28 mL, 0.13 M) was added 10% Pd/C (150 mg) under argon. The atmosphere was replaced with H₂ (balloon pressure) and, after 18 h, the reaction mixture was filtered through celite, washing the celite with EtOAc (3 x 30 mL). The resulting clear and colorless filtrate was concentrated and the product was purified by column chromatography (0–100% gradient of EtOAc in petroleum ether) to give 875 mg (94%) of octyl-D-2-hydroxyglutarate as a white solid:

Rₛ 0.30 (3% MeOH, 0.5% AcOH in CH₂Cl₂)

mp 36.8–37.4°C

¹H NMR (600 MHz, CDCl₃): δ 4.24 (dd, J = 8.0, 4.2 Hz, 1 H), 4.19 (t, J = 6.8 Hz, 2 H), 2.93 (bs, 1 H), 2.56 (ddd, J = 16.8, 8.4, 7.0 Hz, 1 H), 2.49 (ddd, J = 16.8, 8.4, 6.0 Hz, 1 H), 2.19 (dddd, J = 14.1, 8.3, 7.1, 4.2 Hz, 1 H), 1.94 (dddd, J = 14.1, 8.1, 8.1, 6.1 Hz, 1 H), 1.71–1.62 (m, 2 H), 1.40–1.21 (m, 10 H), 0.88 (t, J = 6.8 Hz, 3 H) ppm (supplement figure 3).
$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 178.8, 174.9, 69.5, 66.3, 31.9, 29.5, 29.3 (2 overlapping signals), 29.2, 28.6, 25.9, 22.7, 14.2 ppm (supplement figure 4).

HRMS−TOF ES (m/z): [M + H]$^+$ calcd for C$_{13}$H$_{25}$O$_5$, 261.1702; found, 261.1714.
Supplement figure 3