Three-Component Palladium Catalyzed Synthesis of Functionalized
Bicyclopentanoids

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Supporting Information

Representative coupling of an aryl iodide, a malonate and 1,5-cyclooctadiene (COD):
**2-[(1*RS*, 3*aRS*, 4*SR*, 6*aRS*)-4-(4-Chloro-phenyl)-octahydro-pentalen-1-yl]-
malonic acid dimethylester (4a).**

A mixture of 1-chloro-4-iodobenzene (1.19 g, 5.0 mmol), 1,5-cyclooctadiene (1.25 mL, 10 mmol), dimethyl malonate (2.1 mL, 25 mmol), tetrabutylammonium chloride (1.53 g, 5.5 mmol) and sodium bicarbonate (2.5 g, 30 mmol) in DMSO (15 mL) was heated to 80°C, stirred until homogeneous and tris-(dibenzylideneacetone)-dipalladium (144 mg, 0.25 mmol) was added. The mixture was stirred at 80°C for 20 hours. The mixture was partitioned between ether and water, the combined ether layers were washed with water (3 X) and brine, dried over magnesium sulfate and concentrated to dryness. The product was isolated by flash-chromatography (hexanes / ethyl acetate, 10:1) and obtained as a solid (0.86 g, 49%). ¹H NMR (400 MHz, CDCl₃) δ 1.19-1.27 (m, 1 H), 1.33-1.40 (m, 1 H), 1.47-1.71 (m, 5 H), 1.96 (m, 1 H), 2.35-2.49 (m, 3 H), 2.77 (m, 1 H), 3.37 (d, *J* = 6 Hz, 1 H), 3.73 (s, 3 H), 3.74 (s, 3 H), 7.13 (d, *J* = 8 Hz, 2 H), 7.23 (d, *J* = 9 Hz, 2 H). ¹³C NMR (CDCl₃, 75.5 MHz) δ 27.7 (t), 28.1 (t), 31.0 (t), 35.8 (t), 43.2 (d), 45.7 (d), 51.2 (d), 52.6 (q), 53.4 (d), 54.1 (d), 128.5 (d), 128.7 (d), 131.8 (s), 143.8 (s), 169.3 (s), 169.9 (s). MS (EI) *m/z* 350 (M⁺).

A sample was recrystallized from hexanes and subjected to X-Ray crystallography. Mp 58-60 °C

**2-[(1*RS*, 3*aRS*, 4*SR*, 6*aRS*)-4-(4-Chloro-phenyl)-octahydro-pentalen-1-yl]-
malonic acid dibenzylester (4b).** ¹H NMR (CDCl₃, 400 MHz) δ 1.18 (m, 1 H), 1.34 (m, 1 H), 1.44 (m, 1 H), 1.46-1.64 (m, 5 H), 1.92 (m, 1 H), 2.33-2.40 (m, 2 H), 2.50 (m, 1 H), 2.72 (m, 1 H), 3.44 (d, *J* = 11.6 Hz, 1 H), 5.13 (s, 2 H), 5.15 (s, 1 H), 7.11 (d, *J* = 8.3 Hz, 2 H), 7.23 (d, *J* = 8.3 Hz, 2 H), 7.24-7.35 (m, 11 H). ¹³C NMR (CDCl₃, 100 MHz) δ 27.74, 28.23, 31.01, 35.89, 43.23, 45.75, 51.22, 53.84, 54.12, 67.29, 128.42, 128.44, 128.58, 128.62, 128.78, 128.80, 131.82, 135.57, 135.63, 143.85, 168.70, 169.29. MS (EI) *m/z* 503 (MH⁺)

**2-[(1*RS*, 3*aRS*, 4*SR*, 6*aRS*)-4-(4-Methyl-phenyl)-octahydro-pentalen-1-yl]-
malonic acid dibenzylester (4c).** ¹H NMR (CDCl₃, 300 MHz) δ 1.19 (m, 1 H), 1.34 (m, 1 H), 1.44-1.63 (m, 6 H), 1.91 (m, 1 H), 2.30 (s, 3 H), 2.32-2.53 (m, 3 H), 2.71 (m, 1 H), 3.44 (d, *J* = 11.6 Hz, 1 H), 5.13 (s, 2 H), 5.15 (s, 1 H), 7.09 (s, 4 H), 7.27-7.36 (m, 10 H). ¹³C NMR (100 MHz, CDCl₃) δ 27.7, 29.29, 31.08, 35.97, 43.31, 45.75, 51.20, 53.88, 54.39, 67.25, 127.37, 128.41, 128.44, 128.55, 128.77, 129.25, 135.59, 135.74, 142.36, 168.76, 169.38. MS (EI) *m/z* 481 (M⁺-1), 347 (loss of COOBn).

2-[(1*RS*, 3*aRS*, 4*SR*, 6*aRS*)-4-(Phenyl)-octahydro-pentalen-1-yl]-malonic Acid Dibenzylester (4d). ¹H NMR (CDCl₃, 400 MHz) δ 1.17-1.71 (m, 8 H), 1.93 (dd, *J* = 11.4 Hz, 3.0 Hz, 1 H), 2.38-2.52 (m, 3 H), 2.73 (m, 1 H), 3.45 (d, *J* = 11.6 Hz, 1 H), 5.13 (s, 2 H), 5.16 (s, 1 H), 7.15-7.36 (m, 15 H). ¹³C NMR (100 MHz, CDCl₃) δ 27.80, 28.29, 31.13, 35.93, 43.32, 45.77, 51.23, 52.72, 53.47, 54.81, 126.24, 127.50, 128.57, 145.39, 169.48, 170.08. MS (EI) *m/z* 316 (M⁺).

2-[(1*RS*, 3*aRS*, 4*SR*, 6*aRS*)-[4-(4-Methoxy-phenyl)-octahydro-pentalen-1-yl]-malonic Acid Dimethyl Ester (4e). ¹H NMR (400 MHz, CDCl₃) δ 1.22 (m, 1 H), 1.35 (m, 1 H), 1.45-1.71 (m, 5 H), 1.94 (m, 1 H), 2.35-2.50 (m, 3 H), 2.75 (m, 1 H), 3.37 (d, *J* = 12 Hz, 1 H), 3.73 (s, 3 H), 3.74 (s, 3 H), 3.77 (s, 3 H), 6.82 (d, *J* = 9 Hz, 2 H), 7.13 (d, *J* = 9 Hz, 2 H). ¹³C NMR (100 MHz, CDCl₃) δ 27.79, 28.22, 31.07, 36.06, 43.34, 45.66, 51.27, 52.69, 53.46, 53.99, 55.49, 113.96, 128.32, 137.42, 158.12, 169.49, 170.10. MS (EI) *m/z* 347 (MH⁺).

2-[(1*RS*, 3*aRS*, 4*SR*, 6*aRS*)-4-(4-Acetyl-phenyl)-octahydro-pentalen-1-yl]-malonic Acid Dibenzylester (4f). ¹H NMR (CDCl₃, 300 MHz) δ 1.21 (m, 1 H), 1.36 (m, 1 H), 1.46-1.65 (m, 6 H), 1.96 (m, 1 H), 2.44-2.53 (m, 3 H), 2.56 (s, 3 H), 2.76 (m, 1 H), 3.44 (d, *J* = 11.6 Hz, 1 H), 5.13 (s, 2 H), 5.15 (s, 1 H), 7.27-7.34 (m, 12H), 7.86 (d, *J* = 8.3 Hz, 2 H). ¹³C NMR (100 MHz, CDCl₃) δ 26.82, 27.74, 28.35, 31.06, 35.80, 43.21, 45.87, 51.24, 53.85, 54.79, 67.32, 127.70, 128.44, 128.46, 128.60, 128.79, 129.26, 135.44, 135.56, 135.63, 151.35, 168.68, 169.28, 198.08. MS (EI) *m/z* 509 (M⁺-1).

2-[(1*RS*, 3*aRS*, 4*SR*, 6*aRS*)-4-(1-Naphthyl)-octahydro-pentalen-1-yl]-malonic acid dibenzylester (4g). ¹H NMR (400 MHz, CDCl₃) δ 1.24-1.72 (m, 7 H), 2.08 (m, 1 H), 2.59 (m, 1 H), 2.84 (m, 2 H), 3.33 (m, 1 H), 3.52 (d, *J* = 12 Hz, 1 H), 5.16 (s, 2 H), 5.19 (s, 2 H), 7.28-7.35 (m, 10 H), 7.41-7.50 (m, 4 H), 7.70 (dd, *J* = 7, 3 Hz, 1 H), 7.85 (dd, *J* = 7, 3 Hz, 1 H), 8.11 (d, *J* = 7 Hz, 1 H). MS (EI) *m/z* 519 (MH⁺).

2-[(1*RS*, 3*aRS*, 4*SR*, 6*aRS*)-4-(3-Pyridyl)-octahydro-pentalen-1-yl]-malonic acid dibenzylester (4h). ¹H NMR (CDCl₃, 400 MHz) δ 1.18-1.26 (m, 1 H), 1.31-1.41 (m, 1 H), 1.46-1.67 (m, 5 H), 1.97 (dd, *J* = 11.4 Hz, 5.6 Hz, 1 H), 2.37-2.56 (m, 3 H), 2.76 (m, 1 H), 3.45 (d, *J* = 11.6 Hz, 1 H), 5.13 (s, 2 H), 5.16 (s, 2 H), 7.21 (dd, *J* = 7.9 Hz, 5.0 Hz, 1 H), 7.27-7.33 (m, 10 H), 7.52 (d, *J* = 7.9 Hz, 1 H), 8.42-8.44 (m, 2 H). ¹³C NMR (CDCl₃, 100 MHz) δ 27.71, 28.30, 30.95, 35.67, 43.20, 45.80, 51.09, 52.05, 53.82, 67.32, 67.34, 123.71, 128.44, 128.47, 128.61, 128.80, 134.86, 135.53, 135.61, 140.63, 147.60, 149.16, 168.67, 169.25. MS (EI) *m/z* 470 (MH⁺).

Preparation of 5 and Pd-catalyzed transformation to 6:

(±)-3-(2-Iodo-phenoxy)-cycloocta-1,5-diene (5).

To a solution of cyclooctadien-2,6-dienol (1.5 g, 12 mmol) in DMF (25 mL) was added sodium hydride (0.79 g, 33 mmol) portionwise. After 30 min at room temperature a solution of 2-iodobenzyl bromide (3.26 g in DMF (5 mL) was added.

The reaction mixture was stirred at room temperature overnight then at 60°C for 5 hours, quenched carefully with 1 N HCl, diluted with water and extracted with ethyl acetate (2 X). The combined extracts were washed with water (3 X) and brine, dried over magnesium sulfate and concentrated to dryness. The product was isolated by flash-chromatography (10% ethyl acetate in hexanes) as an oil (2.79 g, 68%). ¹H NMR (CDCl₃, 400 MHz) δ 2.04-2.30 (m, 2 H), 2.35-2.52 (m, 3 H), 2.75 (dd, 1 H), 4.45 (d, 1 H), 4.60 (d, 1 H), 4.82 (dd, 1 H), 5.52-5.70 (m, 4 h), 6.98 (t, 1 H), 7.35 (t, 1 H), 7.44 (t, 1 H), 7.80 (d, 1 H). MS (EI) m/z 340 (M⁺)

2-((6a*RS*, 7a*SR*, 8*RS*, 10a*SR*, 10b*RS*)-6a,7,7a,8,9,10,10a,10b-Octahydro-5*H*-6-oxa-pentaleno[1,2-*a*]naphthalen-8-yl)-malonic acid dimethyl ester (6).

A mixture of (±)-3-(2-iodo-phenoxy)-cycloocta-1,5-diene (0.34 g, 1.0 mmol), dimethyl malonate (0.57 mL, 7.35 mmol), tetrabutylammonium chloride (0.31 g, 1.1 mmol) and sodium bicarbonate (0.21 g, 2.5 mmol) in DMSO (7 mL) was stirred until homogeneous and dipalladium tris(dibenzylideneacetone) (46 mg, 0.05 mmol) was added. The mixture was heated to 70°C for 24 hours then cooled and diluted with ether. The solution was washed with saturated ammonium chloride (3 X), dried over magnesium sulfate and concentrated to dryness. The product was isolated by flash-chromatography (25% ethyl acetate in hexanes) as a solid (0.12 g, 36%). ¹H NMR (CDCl₃, 300 MHz) δ 1.31-1.56 (m, 1 H), 1.68-1.96 (m, 3 H), 2.29-2.44 (m, 4 H), 2.94-3.06 (m, 1 H), 3.35 (d, J = 12 Hz, 1 H), 3.76 (s, 6 H), 4.12 (m, 1 H), 4.71 (AB, J = 12 Hz, 2 H), 6.98 (m, 1 H), 7.11-7.25 (m, 3 H). ¹³C NMR (CDCl₃, 75.5 MHz) δ 27.7 (t), 31.8 (t), 34.5 (t), 42.8 (d), 44.2 (d), 50.2 (d), 50.8 (d), 52.6 (q), 53.5 (d), 80.7 (d), 124.4 (d), 126.1 (d), 126.8 (d), 127.9 (d), 133.1 (s), 137.3 (s), 169.0 (s), 170.0 (s). MS (EI) m/z 344 (M⁺). A sample was recrystallized from ether/hexanes, mp 80-82°C, and subjected to X-ray crystallography.

Pd-catalyzed Reaction of COD and Dimethyl Malonate:

2-[(1*RS*, 3a*RS*, 4*RS*, 6a*RS*)-4-(Bis-methoxycarbonyl-methyl)-octahydro-pentalen-1-yl]-malonic acid dimethyl ester (3).

Dipalladium tris(dibenzylideneacetone) (23 mg, 0.025 mmol) was added to a suspension of 1,5-cyclooctadiene (123 µL, 1.0 mmol), dimethyl malonate (279 µL, 2.4 mmol), and sodium bicarbonate (206 mg, 2.5 mmol) in DMSO (2 mL) in a 15 mL round bottom equipped with a three-way valve attached to an O₂ balloon. The system was evacuated with vacuum and opened to the oxygen. The mixture was stirred at 50°C under O₂ (1 atm) for 20 hours. Water (5mL) was added and the mixture was extracted with ether (5x20mL). The ethereal extracts were combined, dried over magnesium sulfate and concentrated to dryness to yield crude **3** as a yellow oil (492 mg, 132%). Methanol (2 mL) was added to the crude oil and allowed to stand at 0 °C for 16 hours. The methanol was decanted and **3** was isolated as a colorless, crystalline solid (187 mg, 51%). ¹H NMR (CDCl₃, 400 MHz) δ 1.21 (m, 2 H), 1.38 (m, 2 H), 1.55 (m, 2 H), 1.74 (m, 2 H), 2.56-2.63 (m, 4 H), 3.30 (d, J = 11.2 Hz, 2 H), 3.70 (s, 6 H), 3.71 (s, 6 H). ¹³C NMR (CDCl₃, 100 MHz) δ 24.3, 29.8, 43.7, 52.7, 54.3, 169.4, 169.7. MS m/z 371(MH⁺)