

Palladium-Catalyzed Sequential Reaction via Sonogashira Coupling, Isomerization, Claisen Rearrangement and [4+2] Cycloaddition Sequence for the Rapid Synthesis of Tricyclo[3.2.1.0^{2,7}]oct-3-ene Derivatives

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General experimental procedures

General: All reactions were performed under an N₂ atmosphere. Dry solvents were distilled prior to use: THF, toluene and dioxane were distilled from sodium-benzophenone; MeCN was distilled from CaH₂. Petroleum ether refers to the fraction with boiling point in the range 60–90 °C. All ¹H NMR and ¹³C NMR spectra were measured in CDCl₃ or DMSO with TMS as the internal standard. Chemical shifts are expressed in ppm and J values are given in Hz. Starting materials **1** and **2** were prepared according to the known methods.

References:

(a) J. P. Barnier and L. Blanco, *Synthetic Communications*, 2003, **33**, 2487; (b) C. Fu and S. Ma, *Eur. J. Org. Chem.*, 2005, **18**, 3942; (c) A. S. Karpov, E. Merkul, T. Oeser and T. J. J. Müller, *Chem. Commun.*, 2005, 2581.

General Procedure for the Synthesis of Tricyclo[3.2.1.0^{2,7}]oct-3-ene Derivatives **4** via the Palladium-Catalyzed Sequential Reaction of **1** with 1-Aryl Propargyl Trityl Ethers **2**

An oven-dried Schlenk tube containing a Teflon-coated stirring bar was charged with Pd(PPh₃)₂Cl₂ (18 mg, 5 mol %), CuI (3 mg, 3 mol %) and 3-iodocyclohex-2-enone **1a** or other substrates (0.5 mmol). The Schlenk tube was sealed, evacuated and backfilled with N₂ (3 cycles). A solution of 1-aryl propargyl trityl ethers **2** (0.6 mmol) in 6 mL of THF and 2 mL of Et₃N was subsequently injected to the Schlenk tube. The reaction mixture was stirred at 60 °C. After the reaction was complete (monitored by TLC), the reaction was quenched with an aqueous saturated solution of NH₄Cl and extracted with diethyl ether (3 × 20 mL). The combined organic phase was washed with brine and dried over Na₂SO₄. Filtration, evaporation and column chromatography on silica gel (Petroleum ether – ethyl acetate 4:1 to 2:1 v/v) to afford **4**.

(1) 3-[6-Benzhydrylidene-1-(benzoyl) tricyclo[3.2.1.0^{2,7}]oct-3-en-8-yl] cyclohex-2-enone (**4a**)



The reaction of 111 mg (0.5 mmol) of **1a**, 224 mg (0.6 mmol) of **2a**, 18 mg (5 mol %) of Pd(PPh₃)₂Cl₂, and 3 mg (3 mol %) of CuI in 6 mL of THF and 2 mL of Et₃N afforded 171 mg (73%) of **4a**. ¹H NMR (400 MHz, CDCl₃): 7.65-7.64 (m, 2H), 7.50-7.21 (m, 13H), 6.24-6.21 (m, 1H), 5.79 (t, *J* = 8.0 Hz, 1H), 5.73 (s, 1H), 3.54-3.52 (m, 1H), 3.47 (d, *J* = 4.8 Hz, 1H), 3.14 (m, 1H), 2.81 (d, *J* = 8.0 Hz, 1H), 2.22-2.18 (m, 2H), 2.04-2.00 (m, 2H), 1.78-1.75 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): 200.0, 199.2, 161.7, 141.7, 141.6, 138.8, 136.8, 136.0, 131.8, 129.8, 129.7, 128.6, 128.5, 128.2, 128.2, 128.1, 127.6, 127.3, 127.1, 125.6, 125.3, 48.5, 43.1, 42.6, 37.3, 33.5, 29.4, 27.8, 22.4.

IR (KBr): 2916, 1664, 1444, 1261, 1127, 1051 cm^{-1} .

EIMS m/z (%): 468 (M^+ , 12), 105 (100), 165 (48).

HRMS: Calcd for $\text{C}_{34}\text{H}_{28}\text{O}_2$: 468.2089. Found: 468.2094.

(2) 3-[6-Benzhydrylidene-1-(benzoyl) tricyclo[3.2.1.0^{2,7}]oct-3-en-8-yl] 5,5-dimethylcyclohex-2-enone (4b)

The reaction of 125 mg (0.5 mmol) of **1b**, 224 mg (0.6 mmol) of **2a**, 18 mg (5 mol %) of $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, and 3 mg (3 mol %) of CuI in 6 mL of THF and 2 mL of Et_3N afforded 174 mg (70%) of **4b**.

^1H NMR (400 MHz, CDCl_3): 7.63-7.61 (m, 2H), 7.44-7.20 (m, 13H), 6.25-6.21 (m, 1H), 5.79-5.75 (m, 1H), 5.72 (s, 1H), 3.54-3.51 (m, 1H), 3.42 (d, $J = 4.8$ Hz, 1H), 3.20-3.15 (m, 1H), 2.83 (d, $J = 9.2$ Hz, 1H), 2.04 (s, 2H), 1.92-1.81 (m, 2H), 0.86 (s, 3H), 0.74 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): 200.2, 199.3, 159.2, 141.7, 141.6, 139.2, 136.9, 136.0, 131.7, 129.8, 129.8, 128.4, 128.3, 128.2, 127.3, 127.2, 127.2, 126.8, 125.7, 125.2, 51.0, 48.7, 43.6, 43.1, 42.8, 34.0, 33.5, 28.2, 28.0, 27.7.

IR (KBr): 2921, 1661, 1597, 1446, 1262, 1177 cm^{-1} .

EIMS m/z (%): 496 (M^+ , 18), 165 (100), 391 (38).

HRMS: Calcd for $\text{C}_{36}\text{H}_{32}\text{O}_2$: 496.2402. Found: 496.2404.

(3) 3-[6-Benzhydrylidene-1-(4-methylbenzoyl) tricyclo[3.2.1.0^{2,7}]oct-3-en-8-yl]

cyclohex-2-enone (4c)



The reaction of 111 mg (0.5 mmol) of **1a**, 233 mg (0.6 mmol) of **2b**, 18 mg (5 mol %) of Pd(PPh₃)₂Cl₂, and 3 mg (3 mol %) of CuI in 6 mL of THF and 2 mL of Et₃N afforded 190 mg (79%) of **4c**.

¹H NMR (400 MHz, CDCl₃): 7.62-7.60 (m, 2H), 7.37-7.14 (m, 12H), 6.23-6.19 (m, 1H), 5.80-5.75 (m, 2H), 3.56-3.53 (m, 1H), 3.50 (d, *J* = 4.0 Hz, 1H), 3.12-3.08 (m, 1H), 2.76 (d, *J* = 8.0 Hz, 1H), 2.38 (s, 1H), 2.20-2.17 (m, 2H), 2.02-2.00 (m, 2H), 1.77-1.74 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): 199.1, 199.1, 161.7, 142.6, 141.6, 141.5, 136.9, 135.8, 135.7, 129.7, 129.7, 129.1, 128.1, 128.1, 127.6, 127.6, 127.2, 127.0, 125.6, 125.1, 48.7, 43.0, 42.4, 37.2, 33.0, 29.3, 27.3, 22.3, 21.5.

IR (KBr): 2924, 1657, 1604, 1260, 1175, 1125 cm⁻¹.

EIMS *m/z* (%): 482 (M⁺, 20), 119 (100), 165 (80).

HRMS: Calcd for C₃₅H₃₀O₂: 482.2246. Found: 482.2242.

(4) 3-[6-Benzhydrylidene-1-(4-methoxybenzoyl) tricyclo[3.2.1.0^{2,7}]oct-3-en-8-yl] cyclohex-2-enone (4d)

The reaction of 111 mg (0.5 mmol) of **1a**, 242 mg (0.6 mmol) of **2c**, 18 mg (5

mol %) of Pd(PPh₃)₂Cl₂, and 3 mg (3 mol %) of CuI in 6 mL of THF and 2 mL of Et₃N afforded 204 mg (82%) of **4d**.

¹H NMR (400 MHz, CDCl₃): 7.76-7.74 (m, 2H), 7.36-7.21 (m, 10H), 6.94-6.92 (m, 2H), 6.25-6.19 (m, 2H), 5.80-5.78 (m, 3H), 3.86 (s, 3H), 3.57-3.54 (m, 1H), 3.50 (m, 1H), 3.11-3.06 (m, 1H), 2.74-2.72 (m, 1H), 2.21-2.19 (m, 2H), 2.04-2.01 (m, 2H), 1.79-1.76 (m, 2H)

¹³C NMR (100 MHz, CDCl₃): 199.2, 197.5, 162.8, 161.7, 141.7, 141.6, 137.1, 135.8, 130.9, 130.6, 130.0, 129.7, 128.2, 128.1, 127.6, 127.2, 127.1, 125.8, 125.0, 113.7, 55.4, 49.2, 43.2, 42.1, 37.3, 32.6, 29.4, 27.2, 22.4.

IR (KBr): 2926, 1660, 1600, 1254, 1162, 1031 cm⁻¹.

EIMS *m/z* (%): 498 (M⁺, 32), 165 (100), 363 (52).

HRMS: Calcd for C₃₅H₃₀O₃: 498.2195. Found: 498.2199.

(5) 3-[6-Benzhydrylidene-1-(4-fluorobenzoyl) tricyclo[3.2.1.0^{2,7}]oct-3-en-8-yl]cyclohex-2-enone (4e)

The reaction of 111 mg (0.5 mmol) of **1a**, 235 mg (0.6 mmol) of **2d**, 18 mg (5 mol %) of Pd(PPh₃)₂Cl₂, and 3 mg (3 mol %) of CuI in 6 mL of THF and 2 mL of Et₃N afforded 194 mg (80%) of **4e**.

¹H NMR (400 MHz, CDCl₃): 7.74-7.70 (m, 2H), 7.38-7.10 (m, 12H), 6.24-6.21 (m, 1H), 5.80 (t, *J* = 7.6 Hz, 1H), 5.74 (m, 1H), 3.57-3.56 (m, 1H), 3.45 (d, *J* = 5.2 Hz, 1H), 3.12-3.11 (m, 1H), 2.79 (d, *J* = 7.6 Hz, 1H), 2.22-2.19 (m, 2H), 2.03-2.01 (m, 2H), 1.79-1.76 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): 199.1, 198.1, 166.0, 163.5, 161.4, 141.5, 141.4, 136.6, 136.1, 134.8, 134.7, 130.0, 129.9, 129.6, 128.2, 128.1, 127.5, 127.3, 127.2, 125.6,

125.2, 115.7, 115.5, 48.8, 43.0, 42.4, 37.2, 33.3, 29.3, 27.5, 22.3.

IR (KBr): 2945, 1664, 1597, 1498, 1262, 1233 cm^{-1} .

EIMS m/z (%): 486 (M^+ , 15), 123 (100), 363 (38).

HRMS: Calcd for $\text{C}_{34}\text{H}_{27}\text{FO}_2$: 486.1995. Found: 486.1994.

**(6) 3-[6-Benzhydrylidene-1-(4-bromobenzoyl) tricyclo[3.2.1.0^{2,7}]oct-3-en-8-yl]
cyclohex-2-enone (4f)**

The reaction of 111 mg (0.5 mmol) of **1a**, 271 mg (0.6 mmol) of **2e**, 18 mg (5 mol %) of $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, and 3 mg (3 mol %) of CuI in 6 mL of THF and 2 mL of Et_3N afforded 205 mg (75%) of **4f**.

^1H NMR (400 MHz, CDCl_3): 7.61-7.53 (m, 4H), 7.39-7.20 (m, 10H), 6.24-6.21 (m, 1H), 5.80 (t, $J = 6.4$ Hz, 1H), 5.72 (s, 1H), 3.58-3.56 (m, 1H), 3.42 (d, $J = 4.8$ Hz, 1H), 3.13-3.12 (m, 1H), 2.80 (d, $J = 7.6$ Hz, 1H), 2.25-2.10 (m, 2H), 2.06-2.02 (m, 2H), 1.81-1.78 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): 199.2, 198.8, 161.4, 141.5, 141.4, 137.3, 136.4, 136.3, 131.8, 129.7, 128.9, 128.2, 128.2, 127.5, 127.4, 127.2, 126.7, 125.5, 125.2, 48.6, 42.9, 42.4, 37.2, 33.6, 29.3, 27.5, 22.3.

IR (KBr): 2923, 1749, 1660, 1583, 1259, 1127 cm^{-1} .

EIMS m/z (%): 546 (M^+ , 15).

HRMS: Calcd for $\text{C}_{34}\text{H}_{27}\text{BrO}_2$: 546.1194. Found: 546.1198.

**(7) 3-[6-Benzhydrylidene-1-(4-methoxybenzoyl) tricyclo[3.2.1.0^{2,7}]oct-3-en-8-yl]
5,5-dimethylcyclohex-2-enone (4g)**

The reaction of 125 mg (0.5 mmol) of **1b**, 242 mg (0.6 mmol) of **2c**, 18 mg (5 mol %) of Pd(PPh₃)₂Cl₂, and 3 mg (3 mol %) of CuI in 6 mL of THF and 2 mL of Et₃N afforded 216 mg (82%) of **4g**.

¹H NMR (400 MHz, CDCl₃): 7.73-7.71 (m, 2H), 7.38-7.21 (m, 10H), 6.94-6.92 (m, 2H), 6.26-6.23 (m, 2H), 5.79-5.75 (m, 3H), 3.86 (s, 1H), 3.56-3.54 (m, 1H), 3.46 (d, *J* = 4.8 Hz, 1H), 3.14-3.11 (m, 1H), 2.77-2.76 (m, 1H), 2.06 (s, 2H), 1.91 (m, 2H), 0.87 (s, 3H), 0.81 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): 199.4, 197.7, 162.7, 159.4, 141.8, 141.7, 137.2, 135.8, 131.2, 129.9, 129.8, 128.2, 128.2, 127.2, 127.1, 126.8, 125.9, 125.0, 113.7, 55.4, 51.0, 49.2, 43.5, 43.2, 42.4, 33.5, 33.0, 28.0, 27.4.

IR (KBr): 2933, 1747, 1599, 1254, 1026.

EIMS *m/z* (%): 526 (M⁺, 18), 135 (100), 391 (32).

HRMS: Calcd for C₃₇ H₃₄ O₃: 526.2508. Found: 526.2513.

(8) 3-[6-Benzhydrylidene-1-(4-bromobenzoyl) tricyclo[3.2.1.0^{2,7}]oct-3-en-8-yl]-5,5-dimethylcyclohex-2-enone (4h)

The reaction of 125 mg (0.5 mmol) of **1d**, 271 mg (0.6 mmol) of **2e**, 18 mg (5 mol %) of Pd(PPh₃)₂Cl₂, and 3 mg (3 mol %) of CuI in 6 mL of THF and 2 mL of

Et₃N afforded 221 mg (77%) of **4h**.

¹H NMR (400 MHz, CDCl₃): 7.58-7.56 (m, 2H), 7.51-7.49 (m, 2H), 7.38-7.18 (m, 10H), 6.24-6.21 (m, 1H), 5.78-5.74 (m, 1H), 5.70 (s, 1H), 3.55-3.52 (m, 1H), 3.35 (d, *J* = 5.2 Hz, 1H), 3.16 (m, 1H), 2.81 (d, *J* = 7.6 Hz, 1H), 2.06 (s, 2H), 1.89-1.88 (s, 2H), 0.87 (s, 3H), 0.78 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): 199.3, 199.0, 159.0, 141.5, 141.5, 137.6, 136.5, 136.3, 131.7, 129.7, 128.8, 128.3, 128.2, 127.3, 127.2, 126.7, 126.5, 125.6, 125.2, 50.9, 48.7, 43.5, 42.9, 42.7, 34.0, 33.5, 28.1, 27.8, 27.7.

IR (KBr): 2953, 1658, 1583, 1298, 1258, 1170 cm⁻¹.

EIMS *m/z* (%): 574 (M⁺, 11), 165 (100), 391 (44).

HRMS: Calcd for C₃₆H₃₁BrO₂: 574.1507. Found: 574.1502.

(9) 3-[6-Benzhydrylidene-1-(4-methylbenzoyl) tricyclo[3.2.1.0^{2,7}]oct-3-en-8-yl]cyclopent-2-enone (4i)

The reaction of 104 mg (0.5 mmol) of **1c**, 233 mg (0.6 mmol) of **2a**, 18 mg (5 mol %) of Pd(PPh₃)₂Cl₂, and 3 mg (3 mol %) of CuI in 6 mL of THF and 2 mL of Et₃N afforded 176 mg (75%) of **4i**.

¹H NMR (400 MHz, CDCl₃): 7.66-7.64 (m, 2H), 7.39-7.23 (m, 12H), 6.23-6.20 (m, 1H), 5.87-5.84 (m, 2H), 3.64-3.58 (m, 2H), 3.07-3.04 (m, 1H), 2.81-2.79 (m, 1H), 2.41 (s, 1H), 2.30-2.29 (m, 2H), 2.22-2.21 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): 209.4, 198.8, 178.4, 143.1, 141.6, 141.6, 136.7, 136.2, 135.4, 132.1, 129.7, 129.3, 128.2, 128.1, 127.8, 127.3, 127.2, 125.8, 125.5, 46.4, 43.3, 43.0, 35.0, 32.7, 31.1, 26.8, 21.6.

IR (KBr): 2973, 1704, 1650, 1434, 1258, 1127 cm⁻¹.

EIMS *m/z* (%): 468 (M⁺, 13).

HRMS: Calcd for $C_{34}H_{28}O_2$: 468.2089. Found: 468.2087.

**(10) 3-[6-Benzhydrylidene-1-(4-fluorobenzoyl) tricyclo[3.2.1.0^{2,7}]oct-3-en-8-yl]
cyclopent-2-enone (4j)**

The reaction of 104 mg (0.5 mmol) of **1c**, 235 mg (0.6 mmol) of **2d**, 18 mg (5 mol %) of $Pd(PPh_3)_2Cl_2$, and 3 mg (3 mol %) of CuI in 6 mL of THF and 2 mL of Et_3N afforded 184 mg (78%) of **4j**.

1H NMR (400 MHz, $CDCl_3$): 7.78-7.75 (m, 2H), 7.39-7.12 (m, 12H), 6.23-6.20 (m, 1H), 5.87-5.83 (m, 2H), 3.62-3.57 (m, 2H), 3.08-3.05 (m, 1H), 2.82-2.80 (m, 1H), 2.31-2.30 (m, 2H), 2.23-2.22 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 209.3, 197.7, 178.0, 166.3, 163.8, 141.5, 141.5, 136.5, 136.4, 134.3, 134.3, 132.1, 130.2, 130.2, 129.7, 128.3, 128.2, 127.4, 127.3, 125.6, 125.6, 115.9, 115.7, 46.3, 43.2, 42.9, 34.9, 32.8, 31.1, 26.8.

IR (KBr): 2922, 1660, 1259, 1126, 963.

IR (KBr): 2907, 1707, 1664, 1494, 1260, 1149 cm^{-1} .

EIMS m/z (%): 472 (M^+ , 11), 123 (100), 349 (30).

HRMS: Calcd for $C_{33}H_{25}FO_2$: 472.1839. Found: 472.1837.

**(11) 3-[6-Benzhydrylidene-1-(4-bromobenzoyl) tricyclo[3.2.1.0^{2,7}]oct-3-en-8-yl]
cyclopent-2-enone (4k)**

The reaction of 104 mg (0.5 mmol) of **1c**, 271 mg (0.6 mmol) of **2e**, 18 mg (5 mol %) of Pd(PPh₃)₂Cl₂, and 3 mg (3 mol %) of CuI in 6 mL of THF and 2 mL of Et₃N afforded 192 mg (72%) of **4k**.

¹H NMR (400 MHz, CDCl₃): 7.64-7.58 (m, 4H), 7.41-7.22 (m, 10H), 6.25-6.22 (m, 1H), 5.87-5.83 (m, 2H), 3.62-3.56 (m, 2H), 3.10-3.06 (m, 1H), 2.84-2.82 (m, 1H), 2.33-2.32 (m, 2H), 2.26-2.24 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): 209.3, 198.4, 178.0, 141.5, 136.9, 136.6, 136.3, 132.1, 132.0, 129.7, 129.1, 128.3, 128.2, 127.4, 127.3, 127.2, 125.7, 125.6, 46.2, 43.4, 42.9, 35.0, 33.2, 31.1, 26.9.

IR (KBr): 2943, 1707, 1682, 1657, 1491, 1129 cm⁻¹.

EIMS *m/z* (%): 532 (M⁺, 11).

HRMS: Calcd for C₃₃H₂₅BrO₂: 532.1038. Found: 532.1036.

**(12) 3-[6-Benzhydrylidene-1-(4-bromobenzoyl) tricyclo[3.2.1.0^{2,7}]oct-3-en-8-yl]
5,5-dimethylfuran-2(5H)-one (4l)**

The reaction of 119 mg (0.5 mmol) of **1d**, 235 mg (0.6 mmol) of **2d**, 18 mg (5 mol %) of Pd(PPh₃)₂Cl₂, and 3 mg (3 mol %) of CuI in 6 mL of THF and 2 mL of Et₃N afforded 188 mg (75%) of **4l**.

¹H NMR (400 MHz, CDCl₃): 7.68-7.65 (m, 2H), 7.37-7.12 (m, 12H), 6.35 (m, 1H), 5.77 (m, 1H), 5.60 (m, 1H), 3.55 (m, 1H), 3.42-3.41 (m, 1H), 3.13 (m, 1H), 2.90-2.88 (m, 1H), 1.23 (s, 3H), 0.99 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): 197.3, 172.0, 171.2, 166.2, 163.7, 141.3, 141.2, 137.1, 136.4, 134.6, 134.5, 129.9, 129.8, 129.7, 129.6, 128.4, 128.2, 127.6, 127.4, 125.7, 125.5, 118.8, 116.0, 115.7, 86.7, 44.5, 43.4, 40.5, 32.1, 26.6, 24.7, 24.6.

IR (KBr): 2987, 1746, 1672, 1497, 1257, 1153 cm⁻¹.

EIMS *m/z* (%): 502 (M⁺, 15).

HRMS: Calcd for C₃₄H₂₇FO₃: 502.1944. Found: 502.1946.















































