

Supplemental Material

Efficient Construction of the Oxa-tricyclo[6.3.1.0^{0,0}]dodecane Core of Komaroviquinone Using a Cyclization/Cycloaddition Cascade of a Rhodium Carbenoid Intermediate

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Experimental Section

Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70 eV. Unless otherwise noted, all reactions were performed in flame-dried glassware under an atmosphere of dry argon. The microwave reactor and reaction vessels were purchased from CEM Corporation. All solids were recrystallized from ethyl acetate/hexane for analytical data.

α -Methoxycarbonyl- α -diazoacetophenone (7). To a 5.0 g (28 mmol) sample of phthalic acid monomethyl ester was added 24 mL (0.28 mol) of thionyl chloride at rt. The mixture was stirred at rt for 3 h and then the excess thionyl chloride was removed under reduced pressure. The crude residue was redissolved in 200 mL of Et₂O. An ethereal solution of diazomethane, prepared by addition of 32 g (0.15 mol) of diazald (*N*-methyl-*N*-nitroso-*p*-toluenesulfonamide) in 60 mL of Et₂O to 7.7 g (0.14 mol) of potassium hydroxide in 12 mL of water and 37 mL of ethanol, was added to the above acid chloride solution at 0 °C. After the addition was completed, the reaction mixture was allowed to warm up to rt. Silica gel was added, the mixture was stirred for 5 min., filtered, and the solvent was removed under reduced pressure. The crude mixture was purified by flash silica gel column

chromatography using a 40% EtOAc/hexane mixture as the eluent to provide 5.1 g (99%) of the titled compound¹ as a yellow solid: mp 61-62 °C; IR (neat) 3094, 2100, 1726, 1619, and 1352 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 3.88 (s, 3H), 5.58 (brs, 1H), 7.39 (dd, 1H, *J* = 7.2 and 2.0 Hz), 7.44-7.52 (m, 2H) and 7.80 (brs, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ 52.5, 56.1, 126.8, 129.8, 130.3, 130.8, 131.5, 139.6, 167.4 and 188.7.

Methyl 2-(3-oxooct-7-enoyl)benzoate (8). To a solution containing 0.09 g (0.88 mmol) of hex-5-enal² and 0.01 g of SnCl₂ (0.1 mmol) in 1 mL of CH₂Cl₂ was added 0.15 g (0.74 mmol) of the above diazo ketone **7** in 2 mL of CH₂Cl₂. The mixture was stirred at rt for 1 h, diluted with CH₂Cl₂ and washed with water. The organic phase was dried over Na₂SO₄. The solvent was removed under reduced pressure and the crude mixture was purified by flash silica gel column chromatography using a 30% EtOAc/hexane mixture as the eluent to provide 0.04 g (41%) of the titled compound as a yellow oil: IR (neat) 1734, 1727, 1545, 1396, 1292, and 1063 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.81-1.90 (m, 2H), 2.15 (q, 2H, *J* = 6.7 Hz), 2.62 (q, 2H, *J* = 7.6 Hz), 3.87 (s, 3H), 5.00- 5.08 (m, 5H), 5.70-5.82 (m, 1H), 6.28 (s, 1H), 7.57-7.66, (m, 3H) and 7.82- 7.86 (m, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ 24.8, 32.9, 37.2, 53.0, 100.2, 116.3, 129.0, 130.4, 131.4, 132.2, 132.8, 133.3, 136.9, 167.2, 186.4 and 196.8; HRMS Calcd for C₁₆H₁₈O₄: 274.1206. Found: 274.1204.

Methyl 2-(2-Diazo-3-oxooct-7-enoyl)benzoate (9). To a solution containing 0.09 g (0.33 mmol) of the above 1,3-dione **8** in 3.0 mL of CH₃CN was added 0.14 mL (0.98 mmol) of Et₃N and 0.07 g (0.39 mmol) of *p*-nitrobenzenesulfonyl azide³ at rt. The mixture was stirred at rt for 1 h, the solvent was removed under reduced pressure and the crude residue was purified by flash silica gel column chromatography using a 10% EtOAc/hexane mixture as the eluent to provide 0.1 g (98%) of the titled compound as a pale yellow oil: IR (neat) 2120, 1721, 1656 and 1195 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.71-1.77 (m, 2H), 2.09 (q, 2H, *J* = 6.7 Hz), 2.83 (brs, 2H), 3.87 (s, 3H), 4.95 (d, 1H, *J*

= 10.5 Hz), 5.00 (d, 1H, J = 17.1 Hz), 5.71-5.81 (m, 1H), 7.34 (d, 1H, J = 7.6 Hz), 7.54 (td, 1H, J = 7.6 and 1.0 Hz), 7.62 (td, 1H, J = 7.6 and 1.0 Hz) and 8.03 (d, 1H, J = 7.6 Hz); ^{13}C -NMR (100 MHz, CDCl_3) δ 23.1, 33.0, 40.2, 52.6, 85.8, 115.2, 126.3, 127.6, 130.1, 130.6, 132.9, 137.6, 140.5, 165.8, 186.4 and 191.8.

8-Methoxy-12-oxa-tricyclo[6.3.1.0.^{0,0}]octahydro-dibenzo[*a,d*]-4,11-dione (10).

To a solution containing 0.13 g (0.43 mmol) of the above diazodione **9** in 5 mL of benzene was added 0.01 g (0.02 mmol) of $\text{Rh}_2(\text{OAc})_4$ at rt. The mixture was heated for 30 min at 80 °C. The reaction mixture was cooled to rt and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography using a 50% EtOAc/hexane mixture as the eluent to provide 0.03 g (75%) of the titled compound as a pale yellow solid: mp 165-166 °C; IR (neat) 3025, 2910, 1726, 1693, 1600, 1305, and 1281 cm^{-1} ; ^1H -NMR (400 MHz, CDCl_3) δ 1.39-1.52 (m, 1H), 1.92-2.12 (m, 4H), 2.32 (dd, 1H, J = 12.4 and 5.6 Hz), 2.51-2.63 (m, 2H), 2.84-2.95 (m, 1H), 3.50 (s, 3H), 7.42-7.50 (m, 2H), 7.63 (td, 1H, J = 7.3 and 1.3 Hz) and 7.99 (dd, 1H, J = 8.3 and 1.3 Hz); ^{13}C -NMR (100 MHz, CDCl_3) δ 21.7, 28.4, 37.2, 41.9, 42.0, 52.8, 90.1, 106.5, 123.5, 127.5, 128.9, 129.9, 134.5, 144.7, 193.0 and 205.8; Anal. Calcd. for $\text{C}_{16}\text{H}_{16}\text{O}_4$: C, 70.56; H, 5.93.

Found: C, 70.48; H, 5.75.

6a-Hex-5-enoyl-1a-methoxy-1a,6a-dihydro-1-oxa-cyclopropa[*a*]inden-6-one

(12). To a solution containing 0.1 g (0.33 mmol) of the above diazodione **9** in 3 mL of benzene was added 0.01 g (0.02 mmol) of $\text{Rh}_2(\text{OAc})_4$ at rt. The mixture was stirred at rt for 30 min, the solvent was removed under reduced pressure and the crude residue was purified by flash silica gel column chromatography on silica gel to provide 0.054 g (71%) of the titled compound as a pale yellow solid together with 0.009 g (10%) of cycloadduct **10**: IR (neat) 1737, 1724, 1541, 1290, and 1061 cm^{-1} ; ^1H -NMR (400 MHz, CDCl_3) δ 1.67-1.87 (m, 2H), 2.05-2.20 (m, 2H), 2.80-2.99 (m, 2H), 3.42 (s, 3H), 4.94-5.08 (m, 2H), 5.76-5.88 (m, 1H), 7.28 (td, 1H, J = 7.9 and

1.3 Hz), 7.41 (ddd, 2H, $J = 15.9, 7.9$ and 1.0 Hz) and 7.58 (td, 1H, $J = 7.9$ and 1.3 Hz); ^{13}C -NMR (100 MHz, CDCl_3) δ 23.0, 33.0, 40.3, 51.9, 90.3, 99.5, 115.0, 125.6, 127.2, 129.5, 130.1, 134.7, 137.4, 138.3, 187.0 and 197.8; Anal. Calcd. for $\text{C}_{16}\text{H}_{16}\text{O}_4$: C, 70.56; H, 5.93. Found: C, 70.33; H, 5.81.

Heating a sample of epoxide **12** in benzene at $100\text{ }^\circ\text{C}$ for 2 h afforded cycloadduct **10** in 78% yield.

8-Hydroxy-12-oxa-tricyclo[6.3.1.0.^{0,0}]octahydro-dibenzo[*a,d*]-4,11-dione. To a solution containing 0.1 g of **10** in a 1:2:1-mixture of THF/MeOH/ H_2O (2mL) was added 0.5 mL of HCl (conc.). The mixture was heated to reflux for 6 h, cooled and extracted with EtOAc. The combined organic layer was dried over MgSO_4 . The solvent was removed under reduced pressure and the crude mixture was purified by flash silica gel column chromatography using a 50% EtOAc/hexane mixture as the eluent to provide 0.08 g (84%) of the titled compound as a yellow solid: mp $156\text{--}158\text{ }^\circ\text{C}$; IR (KBr) 3425, 2939, 1721, 1692 and 1289 cm^{-1} ; ^1H -NMR (400 MHz, CDCl_3) δ 1.32 (qd, 1H, $J = 12.7$ and 4.8 Hz), 1.86- 2.06 (m, 3H), 1.96 (dd, 1H, $J = 12.0$ and 6.7 Hz), 2.32 (dd, 1H, $J = 12.0$ and 8.6 Hz), 2.38 -2.47 (m, 1H), 2.53 (ddd, 1H, $J = 16.8, 9.5$ and 6.0 Hz), 2.85 (ddd, 1H, $J = 16.8, 11.1$ and 4.8 Hz), 5.79 (s, 1H), 7.28 (td, 1H, $J = 7.6$ and 1.0 Hz) and 7.43 -7.55 (m, 3H); ^{13}C -NMR (100 MHz, CDCl_3) δ 21.8, 28.1, 36.7, 41.9, 43.2, 90.6, 103.6, 123.1, 127.1, 127.5, 128.4, 134.8, 146.7, 192.6 and 207.2; Anal. Calcd. for $\text{C}_{16}\text{H}_{16}\text{O}_4$: C, 69.74; H, 5.47. Found: C, 69.66; H, 5.21.

Ethyl 5-Hydroxy-2,2-dimethylpentanoate. To a stirred solution of 24 mL (12.0 mmol) of 9-BBN (0.5 M in THF) was added a solution of 2.0 g of 2,2 dimethyl-pent-4-enoic acid ethyl ester⁴ (12.0 mmol) in 6 mL of THF at rt. After stirring for 2 h, the reaction was cooled to $0\text{ }^\circ\text{C}$ and 8 mL of ethanol, 2.4 mL of 6 M aq. NaOH solution, and 4.8 mL of 30% aq. H_2O_2 were added consecutively. The mixture was heated at $50\text{ }^\circ\text{C}$ for 1 h. Upon cooling, brine was added and the solution was extracted with

EtOAc. The combined organic layer was dried over MgSO_4 . The solvent was removed under reduced pressure and the crude residue was purified by flash silica gel column chromatography using a 8% EtOAc/hexane mixture as the eluent to provide 1.2 g (55%) of the titled compound as a clear oil; IR (neat) 3467, 2634, 1475, 1280, 1183 and 1055 cm^{-1} ; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.11 (s, 6H), 1.18 (t, 3H, $J = 7.2\text{ Hz}$), 1.47 (m, 4H), 2.06 (s, 1H), 3.53 (t, 1H, $J = 6.0\text{ Hz}$) and 4.06 (q, 2H, $J = 7.2\text{ Hz}$); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 14.1, 25.0, 28.1, 36.5, 41.7, 60.3, 62.8 and 177.9.

Ethyl 5-(*tert*-Butyldimethylsilyloxy)-2,2-dimethylpentanoate. To a solution containing 0.75 g (4.0 mmol) of the above alcohol in 2 mL of DMF was added 0.77 g (10.7 mmol) of imidazole and a crystal of 4-dimethylaminopyridine. The mixture was cooled to $0\text{ }^\circ\text{C}$ for 15 min and then 0.77 g (5.0 mmol) of *tert*-butyldimethylsilyl chloride was added in one portion. The reaction was left to stir for 2 h and then quenched with H_2O and extracted with Et_2O . The combined organic layer was dried over MgSO_4 and the crude residue was purified by flash silica gel column chromatography using a 10% EtOAc/hexane mixture as the eluent to provide 1.0 g (95%) of the titled compound as a clear oil: IR (neat) 2648, 1453, 1265, 1168, 1058 and 1043 cm^{-1} ; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 0.05 (s, 6H), 0.84 (s, 9H), 1.12 (s, 6H), 1.20 (t, 3H, $J = 7.2\text{ Hz}$), 1.47 (m, 4H), 3.54 (t, 2H, $J = 6.0\text{ Hz}$) and 4.08 (q, 2H, $J = 7.2\text{ Hz}$); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ -5.3, 14.1, 25.0, 28.1, 36.5, 41.7, 60.3, 62.8 and 177.9.

Ethyl 5-(*tert*-Butyldimethylsilyloxy)-2,2-dimethylpentanal. To a suspension of 0.13 g (3.0 mmol) of lithium aluminum hydride in 25 mL of Et_2O at $0\text{ }^\circ\text{C}$ was added 0.99 g (3.0 mmol) of the above ester in 10 mL of Et_2O . After stirring for 30 min, the reaction was quenched by the slow addition of 30 mL of H_2O . The aqueous layer was extracted with Et_2O , the solvent was removed under reduced pressure and the crude alcohol was taken up in 15 mL of CH_2Cl_2 . This solution was added to a

stirred solution of 1.1 g (4.5 mmol) of pyridinium chlorochromate in 10 mL of CH_2Cl_2 at rt. The mixture was stirred overnight, filtered and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography using a 10% EtOAc/hexane mixture as the eluent to provide 0.59 g (70%) of the titled compound as a clear oil: IR (neat) 2950, 2919, 1700, 1470, 1383, 1255, 1096 and 830 cm^{-1} ; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 0.01 (s, 6H), 0.85 (s, 9H), 1.15 (s, 6H), 1.52 (m, 4H), 3.60 (t, 2H, $J = 5.7\text{ Hz}$) and 9.39 (s, 1H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ -5.3, 14.1, 24.8, 28.6, 35.1, 42.6, 59.3, 61.4 and 210.3.

***tert*-Butyl-4,4-dimethylhex-5-enyloxyl dimethylsilane.** To a stirred solution of 0.48 g (1.2 mmol) of methyltriphenylphosphonium iodide in 5 mL of THF at $0\text{ }^\circ\text{C}$ was slowly added 0.6 mL (1.2 mmol) of *n*-BuLi (2.1 M in THF). After stirring for 30 min, the solution was warmed to rt and was stirred for an additional 1 h. The mixture was cooled to $0\text{ }^\circ\text{C}$ and a solution of 0.29 g (1.1 mmol) of the above aldehyde in 2 mL of THF was added dropwise and the mixture was allowed to warm to rt and was stirred overnight. The reaction was quenched with H_2O and extracted with Et_2O . The combined organic layer was dried over MgSO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography using a 6% EtOAc/hexane mixture as the eluent to provide 0.23 g (80%) of the titled compound as a clear oil: IR (neat) 2960, 2939, 2863, 1460, 1244 and 1101 cm^{-1} ; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ -0.04 (s, 6H), 0.08 (s, 9H), 0.89 (s, 6H), 1.16 (m, 4H), 3.47 (t, 2H, $J = 6.6\text{ Hz}$), 4.83 (d, 2H, $J = 11.7\text{ Hz}$) and 5.65 (dd, 1H, $J = 10.2\text{ Hz}$); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ -5.3, 14.1, 25.9, 28.1, 36.2, 38.6, 63.8, 110.2 and 132.1.

4,4-Dimethylhex-5-enal. To a solution containing 0.45 g (1.9 mmol) of the above alkene in 8 mL of THF was added 2.3 mL (2.3 mmol) of tetra-butylammonium fluoride (1.0 M in THF) at $0\text{ }^\circ\text{C}$. The reaction mixture was stirred for 2 h after which a 1:1-mixture of H_2O and Et_2O was added to the solution. The aqueous layer was

extracted with Et₂O and the combined organic layer was dried over MgSO₄. The solvent was removed under reduced pressure and the crude alcohol was redissolved in 3 mL of CH₂Cl₂. The mixture was added to a stirred solution of 0.6 g (2.7 mmol) of pyridinium chlorochromate in 2 mL of CH₂Cl₂ at rt. The solution was stirred overnight, filtered and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography using a 6% EtOAc/hexane mixture as the eluent to provide 0.19 g (80%) of the titled compound⁵ as a clear oil: ¹H-NMR (300 MHz, CDCl₃) δ 0.96 (s, 6H), 1.60 (t, 2H, *J* = 8.4 Hz), 2.20 (t, 2H, *J* = 8.4 Hz), 4.90 (dd, 2H, *J* = 9.3 Hz) and 5.66 (dd, 1H, *J* = 11.1 Hz); ¹³C-NMR (75 MHz, CDCl₃) δ 26.3, 26.4, 29.8, 36.1, 36.6, 111.4, 146.8 and 180.2.

Methyl 2-(6,6-Dimethyl-3-oxo-oct-7-enyl)benzoate. To a solution containing 0.34 g (1.6 mmol) of diazo ketone **7** and 0.03 g (0.16 mmol) of anhydrous SnCl₂ in 4 mL of CH₂Cl₂ was added a solution of 0.25 g (1.9 mmol) of the above aldehyde in 4 mL of CH₂Cl₂ and the mixture was stirred at rt for 18 h. The solution was quenched with H₂O and extracted with Et₂O. The combined organic layer was dried over MgSO₄ and the crude residue was purified by flash silica gel column chromatography using a 20% EtOAc/hexane mixture as the eluent to provide 1.0 g (20%) of the titled compound as a clear oil: IR (neat) 3210, 2113, 1721, 1700, 1588 and 1434 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 1.00 (s, 6H), 1.64 (m, 2H), 2.28 (m, 2H), 3.83 (s, 3H), 4.96 (m, 2H), 5.75 (t, 1H, *J* = 8.1 Hz), 5.81 (s, 1H) and 7.52 (s, 4H); ¹³C-NMR (75 MHz, CDCl₃) δ 26.5, 33.9, 36.4, 38.0, 52.5, 98.9, 111.5, 127.9, 129.5, 130.5, 131.1, 137.5, 147.1, 188.4 and 194.4; HRMS Calcd for C₁₈H₂₂O₄: 302.1518. Found: 302.1516.

Methyl 2-(2-diazo-6,6-dimethyl-3-oxooct-7-enyl)benzoate (13). To a solution containing 1.0 g (0.32 mmol) of the above diketoester and 0.11 g (0.44 mmol) of *p*-nitrobenzenesulfonyl azide³ in 3 mL of CH₃CN at 0 °C was added 0.09 g (0.65

mmol) of Et₃N. The reaction mixture was stirred for 3 h, the solvent was removed under reduced pressure and the crude residue was purified by flash silica gel column chromatography using a 50% EtOAc/hexane mixture as the eluent to provide 0.4 g (38%) of the titled compound as a clear oil: IR (neat) 3105, 2921, 2131, 1712, 1656 and 1534 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 0.86 (s, 6H), 1.52 (m, 2H), 2.54 (m, 2H), 3.76 (s, 3H), 4.79 (m, 2H), 5.59 (dd, 1H, *J* = 6.6 Hz), 7.49 (dt, 2H, *J* = 8.1 Hz), 8.05 (d, 1H, *J* = 8.4 Hz) and 8.35 (d, 1H, *J* = 9 Hz); ¹³C-NMR (75 MHz, CDCl₃) δ 26.4, 35.9, 36.2, 36.9, 52.6, 111.3, 124.9, 126.4, 127.7, 128.8, 130.1, 130.6, 132.9, 147.1 and 165.8.

1,1-Dimethyl-8-methoxy-12-oxa-tricyclo[6.3.1.0.^{0,0}]octahydro-dibenzo[*a,d*]-4,11-dione (14). To a solution containing 0.04 g (0.12 mmol) of diazo-dione **13** in 1 mL of benzene was added 0.004 g (0.01 mmol) of Rh₂(OAc)₄. The mixture was heated at 80 °C for 18 h. The solution was filtered and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography using a 6% EtOAc/hexane mixture as the eluent to provide 0.012 g (92%) of the titled compound as a clear oil; IR (neat) 1682, 1623, 1269, 1058 and 1009 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 0.92 (s, 6H), 1.80 (dd, 1H, *J* = 7.2 Hz), 1.93 (m, 1H), 2.07 (t, 1H, *J* = 9.0 Hz), 2.18 (dd, 1H, *J* = 9.0 Hz), 2.39 (t, 1H, *J* = 6.3 Hz), 2.64 (m, 1H), 2.78 (dd, 1H, *J* = 7.2 Hz), 3.49 (s, 3H), 7.45 (t, 2H, *J* = 5.4 Hz), 7.64 (t, 1H, *J* = 5.4 Hz) and 7.97 (d, 1H, *J* = 5.7 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ 20.2, 29.7, 32.9, 35.7, 36.1, 36.4, 51.4, 52.7, 88.6, 106.5, 123.6, 127.4, 128.9, 129.6, 134.4, 144.6, 193.1 and 206.7; HRMS (FAB) Calcd for [(C₁₈H₂₀O₄)+Li]⁺: 300.1361. Found 300.1373.

References:

1. (a) Dugggleby, P. M.; Holt, G. *J. Chem. Soc.* **1962**, 3579. (b) Ueda, K.; Ibata, T.; Takebayashi, M. *Bull. Chem. Soc. Jpn.* **1972**, 45, 2779. (c) Hodson, D.; Holt, G.; Wall, D.K. *J. Chem. Soc. C* **1970**, 971.

2. (a) Banwell, M. G.; Bissett, B. D.; Bui, C. T.; Pham, H. T. T.; Simpson, G. W. *Aust. J. Chem.* **1998**, *51*, 9. (b) Meyer, C.; Marek, I.; Courtemanche, G.; Normant, J.-F. *Tetrahedron* **1994**, *50*, 1165. (c) Miyata, O.; Muroya, K.; Kobayashi, T.; Yamanaka, R.; Kajisa, S.; Koide, J.; Naito, T. *Tetrahedron* **2002**, *58*, 4459.
3. Reagan, M. T.; Nickon, A. *J. Am. Chem. Soc.* **1968**, *90*, 4096.
4. Baldwin, J. E.; Walker, J. E. *J. Chem. Soc. Chem. Comm.*, **1973**, 117.
5. Kossanyi J.; Guiard, B.; Furth, B. *Bull. Soc. Chem. Fr.*, **1974**, 305.

