Tandem Sequence of Cross Metathesis–Ring-Closing Metathesis Reaction of Alkynyl Silyloxy-Tethered Enynes

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Materials and Methods

^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-250 or a Bruker AC-300 spectrometer. Tetramethylsilane (TMS) or CDCl_3 served as internal standard ($\delta = 0$ or 7.26 respectively) for ^1H NMR. CDCl_3 was used as internal standard ($\delta = 77.2$) for ^{13}C NMR. All reactions were run under an atmosphere of nitrogen, unless otherwise indicated. Infrared spectra (IR) were obtained on a FT-IR equipped with a DTGS detector. Flasks were oven-dried overnight and cooled under a stream of nitrogen. Compounds were purchased from Aldrich. Dichloromethane was distilled from CaH_2 . All other solvents were purified based on standard procedures. Flash chromatography was performed using silica gel 60 Å (32-63 mesh) from Sorbent Technologies. Reactions were monitored by thin layer chromatography (TLC) using 0.25 mm E. Merk pre-coated silica gel 60 (particle size 0.040 – 0.063 mm).

Representative Procedure for a Tandem CM-RCM Reaction of 9a-f

Silyated enyne **9b** (34 mg, 0.101 mmol) and 5-hexenyl-1-acetate (57 mg, 0.401 mmol) were dissolved in freshly distilled CH_2Cl_2 (0.03 M). Grubbs 2nd generation catalyst **1**, $(\text{H}_2\text{Imes})(\text{PCy}_3)\text{Cl}_2\text{Ru}=\text{CHPh}$, (6 mg, 0.007 mmol) was added to the reaction mixture. After stirring under reflux for 4 h, the reaction mixture was concentrated and the residue was purified by flash column chromatography (hexanes/EtOAc 20:1) to yield the desired CM-RCM product **10b** (oil, 21 mg, 46%).

Desilylation of 10a

To a solution of compound **10a** (35 mg, 0.073 mmol) in THF, was added *n*-BuN₄F (1.0 M in THF, 0.10 mL) at room temperature. After stirring for 4 h, the reaction mixture was concentrated under reduced pressure and the residue was directly purified by flash column chromatography (hexanes/EtOAc 5:1) to afford the desilylated product **10aa** (oil, 21 mg, 96%). **¹H NMR (300 MHz, CDCl₃):** δ 6.30 (d, *J* = 15.8 Hz, 1H), 5.84 (dt, *J* = 15.8, 7.0 Hz, 1H), 5.47 (d, *J* = 8.8 Hz, 1H), 4.57 (dt, *J* = 8.8, 6.8 Hz, 1H), 4.06 (t, *J* = 6.8 Hz, 2H), 4.03 (m, 2H), 3.32 (s, 3H), 2.16 (q, *J* = 7.3 Hz, 3H), 2.04 (s, 3H), 1.57-1.69 (m, 4H, overlap), 1.42-1.54 (m, 4H, overlap), 1.22-1.40 (m, 4H, overlap), 0.89 (t, *J* = 6.8 Hz, 3H); **¹³C NMR (75 MHz, CDCl₃):** δ 171.44, 134.52, 132.90, 132.76, 124.80, 74.63, 67.64, 64.53, 58.02, 37.43, 33.18, 28.29, 27.71, 25.68, 22.85, 21.20, 14.24; **HRMS (ESI)** calcd for C₁₇H₃₀O₄Na [M+Na]⁺: 321.2042, found. 321.2037.

¹H NMR (300 MHz, CDCl₃): δ 7.68 (m, 5H), 7.37 (m, 6H), 7.24 (m, 5H), 6.31 (t, *J* = 7.5 Hz, 1H), 6.22 (d, *J* = 15.7 Hz, 1H), 6.02 (dd, *J* = 15.9, 6.9 Hz, 1H), 4.96 (d, *J* = 2.0 Hz, 1H), 4.92 (d, *J* = 2.0 Hz, 1H), 4.34 (q, *J* = 6.4 Hz, 1H), 3.85 (s, 2H), 3.79 (t, *J* = 6.6 Hz, 2H), 3.15 (s, 3H), 2.02 (t, *J* = 9.0 Hz, 2H), 1.97 (s, 3H), 1.66-1.41 (m, 4H), 1.37-1.11 (m, 6H), 0.89 (m, 3H); **¹³C NMR (75 MHz, CDCl₃):** δ 171.26, 151.73, 148.74, 135.59, 135.50, 135.30, 132.74, 129.99, 129.91, 128.61, 127.93, 127.84, 127.46, 126.56, 111.17, 75.62, 75.07, 57.98, 37.90, 32.63, 28.29, 27.27, 25.79, 25.69, 22.82, 21.17, 14.24; **IR** (thin film) 2927, 1739, 1429, 1240, 1114 cm⁻¹; **HRMS (EI)** calcd for C₃₇H₄₆O₄Si [M]⁺: 582.3165, found 582.3144.

¹H NMR (300 MHz, CDCl₃): δ 7.67 (m, 4H), 7.41 (m, 6H), 6.64 (q, J = 7.2 Hz, 1H), 5.73 (d, J = 2.8 Hz, 1H), 4.60 (brq, 1H), 4.20 (m, 2H), 3.36 (s, 3H), 1.63 (d, J = 7.1 Hz, 3H), 1.14-1.60 (m, 6H), 0.83 (t, J = 7.1 Hz, 3H); **¹³C NMR (75 MHz, CDCl₃):** δ 137.41, 135.42, 135.36, 132.01, 130.22, 128.39, 128.12, 128.03, 75.33, 72.75, 57.85, 38.31, 27.54, 22.78, 19.87, 14.21; **IR** (thin film) 2923, 2174, 1430, 1373, 1114 cm⁻¹; **HRMS (EI)** calcd for C₂₄H₃₀O₂Si [M]⁺: 378.2015, found 378.1997.

¹H NMR (300 MHz, CDCl₃): δ 7.64 (td, J = 7.7, 1.5 Hz, 4H), 7.36 (m, 6H), 6.52 (t, J = 7.7 Hz, 1H), 4.56 (q, J = 6.7 Hz, 1H), 4.27 (d, J = 10.5 Hz, 1H), 4.16 (d, J = 10.5 Hz, 1H), 3.74 (t, J = 6.3 Hz, 2H), 3.36 (s, 3H), 1.96 (s, 3H), 1.93-2.01 (m, 2H, overlap), 1.81 (s, 3H), 1.31 (d, J = 6.7 Hz, 3H), 1.03-1.25 (m, 6H); **¹³C NMR (75 MHz, CDCl₃):** δ 171.20, 141.37, 136.25, 135.47, 135.28, 130.47, 130.20, 129.13, 128.07, 74.80, 70.53, 64.48, 57.92, 33.67, 28.24, 26.05, 24.11, 21.14, 18.58; **IR** (thin film) 2927, 1739, 1429, 1241, 1094 cm⁻¹; **HRMS (EI)** calcd for C₂₆H₃₁O₄Si [M-CH₃]⁺: 435.1992, found 435.1996.

¹H NMR (300 MHz, CDCl₃): δ 7.63 (m, 4H), 7.31-7.41 (m, 6H), 6.52 (t, J = 7.7 Hz, 1H), 5.14 (t, J = 6.7 Hz, 1H), 4.43 (dd, J = 8.4, 3.5 Hz, 1H), 4.29 (d, J = 10.6 Hz, 1H), 4.16 (d, J = 10.6 Hz, 1H), 3.74 (t, J = 6.5 Hz, 2H), 3.34 (s, 3H), 2.36-2.47 (m, 1H), 2.05-2.18 (m, 1H), 1.96 (s, 3H), 1.92-2.04 (m, 2H, overlap), 1.83 (s, 3H), 1.40 (s, 6H), 1.02-1.25 (m, 2H), 1.31 (d, J = 6.7 Hz, 3H), 1.03-1.25 (m, 5H), 0.89 (m, 1H); **¹³C NMR (75 MHz, CDCl₃):** δ 171.30, 141.37, 140.17, 135.60, 135.31, 133.24, 131.38, 130.09, 129.35, 127.95, 121.20, 79.13, 70.50, 64.50, 57.81, 36.20, 33.63, 28.22, 26.09, 25.94, 21.15, 18.89, 18.00; **HRMS (EI)** calcd for C₂₆H₃₁O₄Si [M-C₄H₇]⁺: 435.1992, found 435.2011.

^1H NMR (300 MHz, CDCl_3): δ 7.59-7.69 (m, 4H), 7.34-7.45 (m, 6H), 6.67 (q, J = 7.2 Hz, 1H), 4.29-4.33 (m, 1H, overlap), 4.29 (d, J = 10.7 Hz, 1H, overlap), 4.15 (d, J = 10.7 Hz, 1H), 3.36 (s, 3H), 1.82 (s, 3H), 1.60-1.78 (m, 1H, overlap), 1.64 (d, J = 7.2 Hz, 3H), 1.34-1.51 (m, 1H), 0.81 (t, J = 7.2 Hz, 3H); **^{13}C NMR (75 MHz, CDCl_3):** δ 139.96, 136.33, 136.16, 135.48, 135.31, 130.08, 129.92, 128.03, 80.26, 70.55, 57.90, 30.32, 20.01, 18.79, 10.49; **HRMS (EI)** calcd for $\text{C}_{23}\text{H}_{28}\text{O}_2\text{Si}$ $[\text{M}]^{+}$: 364.1859, found 364.1847.

Compound 10e. **^1H NMR (250 MHz, CDCl_3):** δ 6.31 (d, J = 15.4 Hz, 1H), 5.85 (dt, J = 15.4, 7.3 Hz, 1H), 5.48 (d, J = 9.2 Hz, 1H), 5.38 (m, 2H), 4.58 (br dt, 1H), 4.00-4.10 (m, 6H, overlap), 3.32 (s, 3H), 1.95-2.21 (m, 6H, overlap), 2.04 (s, 6H), 1.21-1.70 (m, 12H, overlap); **^{13}C NMR (62 MHz, CDCl_3):** δ 171.47, 134.70, 132.89, 132.73, 130.72, 129.77, 124.82, 76.12, 74.62, 69.04, 67.53, 64.71, 58.09, 37.19, 33.22, 32.30, 28.33, 25.72, 25.49, 21.23; **HRMS (ESI)** calcd for $\text{C}_{24}\text{H}_{40}\text{O}_6\text{Na}$ $[\text{M}+\text{Na}]^{+}$: 447.2723, found 447.2729.

^1H NMR (300 MHz, CDCl_3): δ 7.64-7.68 (m, 4H), 7.36-7.49 (m, 6H), 6.72 (brs, 1H), 6.40 (d, J = 16.0 Hz, 1H), 5.61 (dt, J = 15.5, 6.9 Hz, 1H), 5.04 (brq, J = 6.6 Hz, 1H), 3.99 (t, J = 6.5 Hz, 2H), 2.02-2.11 (m, 2H, overlap), 2.03 (s, 3H, overlap), 1.49-1.58 (m, 2H), 1.31-1.44 (m, 2H), 1.42 (d, J = 6.7 Hz, 3H); **^{13}C NMR (75 MHz, CDCl_3):** δ 171.47, 149.60, 137.28, 136.42, 135.39, 134.44, 130.56, 129.28, 128.14, 78.59, 64.50, 32.59, 28.13, 25.61, 23.74, 21.19; **HRMS (EI)** calcd for $\text{C}_{24}\text{H}_{28}\text{O}_3\text{Si}$ $[\text{M}]^{+}$: 392.1808, found 392.1799.

Compound 10g. $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 6.35 (dd, $J = 15.2, 12.3$ Hz, 1H), 5.96 (t, $J = 10$ Hz, 1H), 5.71 (dt, $J = 14.8, 7.1$ Hz, 1H), 5.34 (dd, $J = 9.8, 9.7$ Hz, 1H), 4.79 (dq, $J = 8.7, 6.3$ Hz, 1H), 4.06 (t, $J = 6.6$ Hz, 2H), 2.24 (q, $J = 7.2$ Hz, 2H), 2.05 (s, 3H), 1.58-1.70 (m, 2H), 1.40-1.53 (m, 2H), 1.28 (d, $J = 6.3$ Hz, 3H); $^{13}\text{C NMR}$ (62 MHz, CDCl_3): δ 171.35, 136.50, 133.10, 129.62, 125.69, 64.53, 64.30, 32.53, 28.30, 25.66, 23.74, 21.23; **IR** (thin film) 3407, 2097, 1740, 1242, 1059 cm^{-1} ; **HRMS (ESI)** calcd for $\text{C}_{12}\text{H}_{20}\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^{+}$: 235.1310, found 235.1308.

CM Reaction of 2a with *cis*-2-Butene

Silylated enyne **2a** (37 mg, 0.102 mmol) was dissolved in freshly distilled CH_2Cl_2 (0.03 M). Grubbs 2nd generation catalyst **1** (9 mg, 0.011 mmol) was added to the reaction mixture. *cis*-2-Butene was added by bubbling into the solution throughout the reaction. After stirring under reflux for 6 h, the reaction mixture was concentrated and the residue was purified by flash column chromatography (hexanes/EtOAc 20:1) to yield the desired CM-RCM product **12** (oil, 18 mg, 42%).

Compound 12. $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 6.30 (d, $J = 17.1$ Hz, 1H), 5.90 (dq, $J = 15.9, 6.6$ Hz, 1H), 5.45 (d, $J = 8.9$ Hz, 1H), 5.20 (brs, 1H), 4.59 (brs, 1H), 4.06 (d, $J = 11.7$ Hz, 1H), 4.00 (d, $J = 11.7$ Hz, 1H), 3.32 (s, 3H), 2.02 (dt, $J = 16.0, 6.4$ Hz, 2H), 1.81 (dd, $J = 6.6, 1.8$ Hz, 3H), 1.39-1.70 (m, 7H), 1.57 (s, 3H, overlap); $^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ 134.73, 132.38, 128.44, 125.61, 119.46, 118.84, 74.74, 67.59, 58.10, 39.66, 37.21, 23.76, 19.18, 15.65, 13.54; **HRMS (EI)** calcd for $\text{C}_{15}\text{H}_{26}\text{O}_2$ $[\text{M}]^{+}$: 238.1933, found 238.1939.

CM-RCM Reaction of 2a with 1,5-Cyclooctadiene

Silyated enyne **2a** (52 mg, 0.143 mmol) and 1,5-cyclooctadiene (31 mg, 0.287 mmol) were dissolved in freshly distilled CH₂Cl₂ (0.03 M). Grubbs 2nd generation catalyst **1** (10 mg, 0.012 mmol) was added to the reaction mixture. After stirring under reflux for 6 h, the reaction mixture was concentrated and the residue was purified by flash column chromatography (hexanes/EtOAc 20:1) to yield the desired CM-RCM product **13** (oil, 32 mg, 54%).

¹H NMR (300 MHz, CDCl₃): δ 7.64-7.71 (m, 4H), 7.33-7.44 (m, 6H), 6.46 (m, 1H), 5.90 (m, 1H), 5.39 (m, 1H), 4.41 (m, 1H), 3.85 (s, 2H), 2.95 (s, 3H), 2.15 (m, 4H), 1.40-2.10 (m, 6H, overlap), 1.64 (s, 3H, overlap); **¹³C NMR (75 MHz, CDCl₃):** δ 144.49, 137.45, 136.28, 136.13, 135.61, 132.66, 129.65, 127.75, 125.24, 122.67, 74.82, 68.01, 57.74, 32.04, 30.26, 23.86, 23.83, 21.85, 19.74; **IR** (thin film) 3050, 2932, 1429, 1265, 1114, 909 cm⁻¹; **HRMS (ESI)** calcd for C₂₇H₃₂O₂SiNa [M+Na]⁺: 439.2069, found 439.2064.

¹H NMR (300 MHz, CDCl₃): δ 7.63-7.67 (m, 4H), 7.34-7.48 (m, 6H), 6.48 (t, *J* = 7.8 Hz, 1H), 5.73 (d, *J* = 2.2 Hz, 1H), 4.75 (q, *J* = 6.4 Hz, 1H), 4.19 (s, 2H), 3.74 (t, *J* = 6.4 Hz, 2H), 3.36 (s, 3H), 1.94-2.01 (m, 2H, overlap), 1.97 (s, 3H), 1.32 (d, *J* = 6.7 Hz, 3H), 1.00-1.21 (m, 4H); **¹³C NMR (75 MHz, CDCl₃):** δ 171.34, 142.19, 135.38, 134.62, 133.08, 130.35, 128.17, 128.07, 127.39, 75.04, 69.07, 64.42, 57.92, 33.70, 28.19, 25.81, 24.90, 21.17; **HRMS (EI)** calcd for C₂₆H₃₂O₄Si [M]⁺: 436.2070, found 436.2087.

Representative Procedure for a CM Reaction of 49a-f

Silyated enyne **49d** (33 mg, 0.102 mmol) and 5-hexenyl-1-acetate (57 mg, 0.401 mmol) were dissolved in freshly distilled CH₂Cl₂ (0.03 M). Grubbs 2nd generation catalyst **1** (10 mg, 0.012 mmol) was added to the reaction mixture. After stirring under reflux for 4 h, the reaction mixture was concentrated and the residue was purified by flash column chromatography (hexanes/EtOAc 20:1) to yield the desired CM product **50d** (oil, 38 mg, 82%).

¹H NMR (300 MHz, CDCl₃): _ 7.65-7.68 (m, 4H), 7.35-7.45 (m, 6H), 6.34 (t, *J* = 7.7 Hz, 1H), 4.95 (brs, 1H), 4.93 (brs, 1H), 3.84 (t, *J* = 6.4 Hz, 2H), 3.83 (s, 2H), 3.62 (t, *J* = 6.6 Hz, 2H), 3.17 (s, 3H), 2.04 (m, 2H, overlap), 1.99 (s, 3H), 1.53 (sextet, *J* = 7.1 Hz, 2H), 1.15-1.38 (m, 4H), 0.85 (t, *J* = 7.3 Hz, 3H) ; **¹³C NMR (75 MHz, CDCl₃):** 171.29, 151.40, 148.92, 137.64, 135.32, 129.97, 127.96, 111.19, 75.52, 65.56, 64.51, 57.94, 32.45, 28.33, 25.84, 25.80, 21.13, 10.56; **HRMS (ESI)** calcd for C₂₇H₃₆O₄SiNa [M+Na]⁺: 475.2281, found 475.2258.

¹H NMR (300 MHz, CDCl₃): _ 7.63-7.67 (m, 4H), 7.36-7.48 (m, 6H), 6.49 (t, *J* = 7.7 Hz, 1H), 5.79 (t, *J* = 3.2 Hz, 1H), 4.62 (s, 2H), 4.20 (d, *J* = 1 Hz, 2H), 3.74 (t, *J* = 6.4 Hz, 2H), 3.36 (s, 3H), 1.95-2.07(m, 2H, overlap), 1.97 (s, 3H), 1.04-1.25(m, 4H); **¹³C NMR (62 MHz, CDCl₃):** 171.35, 142.22, 135.47, 135.34, 134.62, 134.54, 130.64, 130.49, 128.17, 74.93, 64.39, 63.60, 57.88, 33.67, 28.18, 25.82, 21.13; **HRMS (ESI)** calcd for C₂₅H₃₀O₄SiNa [M+Na]⁺: 445.1811, found 445.1832.