An Expeditious Route to Eight and Nine-membered Carbocycles based on a RCM-Ring Fragmentation Strategy

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SUPPORTING INFORMATION

EXPERIMENTAL SECTION

General Procedures. All dry solvents were freshly distilled under argon from an appropriate drying agent before use. Toluene and THF were distilled from sodium/benzophenone ketyl. CH_2Cl_2 and Et_3N were distilled from CaH_2. MeOH was distilled from Mg/I_2. Allyl bromide was distilled from P_2O_5. All reactions were conducted in dry solvents under argon atmosphere unless otherwise stated. External bath temperatures were used to record all reaction temperatures. Melting points (open capillary tubes) are uncorrected. Thin-layer chromatography (TLC) was performed on silica gel plates and components were visualized by observation under UV light, or by treating the plates with a phosphomolybdic reagent followed by heating. Dryings were performed with anhydrous Na_2SO_4. Concentration refers to the removal of volatile solvents via distillation using a Buchi rotary evaporator at water aspirator pressure, followed by residual solvent removal at high vacuum (aprox. 0.5 mmHg). Vinyllithium (0.45 M in Et_2O/pentane) was freshly prepared from vinylbromide by treatment with *t*-BuLi (1.5 M in pentane). Allyllithium (0.35 M in THF) was freshly prepared from allyltriphenyltin and phenyllithium. The TBAF used was 1M in THF.

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, at 250 MHz and 62.9 MHz, respectively, and in some cases at 300 or 500 MHz (75.4 or 125.7 for ^{13}C NMR) Carbon types were determined from DEPT ^{13}C NMR experiments. The following abbreviations are used to indicate signal multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

Synthesis of silylated cyclohexenones 1

To a solution of 1,2-cyclohexanedione (225 mg, 2 mmol) in CH_2Cl_2 (20 mL) were added imidazole (204 mg, 3 mmol) and the corresponding silyl chloride (2.3 mmol). The mixture was stirred at rt for 30 min and poured into NaOH (10% aqueous solution). Extraction with CH_2Cl_2, drying, filtering and concentration gave a residue that was purified by flash cromatography on silica gel (3% EtOAc/hexanes) to afford the protected compounds in almost quantitative yields.

Compound **1a**: R_f= 0.66 (20% EtOAc/hexanes), colorless oil.

^1H NMR δ (ppm): 6.11 (1H, t, *J* = 4.56 Hz), 2.43-2.19 (4H, m), 1.9 (2H, m), 0.88 (9H, s), 0.085 (6H, s).

^{13}C NMR δ (ppm): 195.4 (C), 147.9 (C), 127.5 (CH), 38.6 (CH_2), 25.6 (CH_3), 24.7 (CH_2), 23.1 (CH_2), 18.3 (C), -4.8 (CH_3).

LRMS (*m/z*): 169 [M^+-$C(CH_3)_3$, 100], 139 (11), 111 (6), 95 (4).

HR-FABMS+ calcd. for $C_{12}H_{22}O_2Si$ 227.1467, found 227.1467.

Compound **1c**: R_f= 0.82 (20% EtOAc/hexanes), colorless oil

^1H NMR δ (ppm): 6.12 (1H, t, *J* = 4.6 Hz), 2.44 (2H, m), 2.35 (2H, m), 1.9 (2H, m), 1.15 (3H, m), 1.02 (18H, m).

^{13}C NMR δ (ppm): 195.3 (C), 148.4 (C), 126.4 (CH), 38.8 (CH_2), 24.8 (CH_2), 23.1 (CH_2), 17.9 (CH_3), 17.6 (CH_3), 12.8 (CH), 12.3 (CH).

LRMS (*m/z*): 268 (M^+, 7), 256 (100), 213 (41), 169 (25), 157 (40), 153 (26), 118 (53)

HR-FABMS+ calcd. for $C_{15}H_{29}O_2Si$ 269.1936, found 269.1924.

Compound **1d**: R_f= 0.74 (25% EtOAc/hexanes), colorless oil

^{1}H NMR δ (ppm): 7.71 (4H, m), 7.41 (6H, m), 5.94 (1H, t, *J* = 4.3 Hz), 2.35 (2H, t, *J* = 6.6 Hz), 2.17 (2H, m), 1.81 (2H, m), 1.11 (9H, s).

^{13}C NMR δ (ppm): 194.7 (C), 147.7 (C), 135.5 (CH), 133.0 (C), 129.7 (CH), 127.5 (CH), 127.3 (CH), 38.6 (CH_2), 26.6 (CH_3), 24.6 (CH_2), 22.9 (CH_2), 19.5 (C).

LRMS (*m/z*): 350 (M^+, 0.02), 293 [M^+-$C(CH_3)_3$, 100], 273 (5), 215 (9), 189 (13), 139 (7).

HR-FABMS+ calcd. for $C_{22}H_{27}O_2Si$ 351.1780, found 351.1775.

Procedure for the addition-alkylation-desilylation sequence

A solution of **1d** (700 mg, 2 mmol) in THF (20 mL) was cooled at –78°C and vinyllithium (4.9 mL, 2.2 mmol, 0.45 M in Et_2O/pentane) was added. The reaction was allowed to reach rt and stirred for 1h. After recooling to –78°C, allyl bromide (0.26 mL, 3 mmol) was added and the mixture stirred overnigth at that temperature. TBAF (3 mL, 3 mmol, 1M in THF) was added and the resulting solution stirred for 1 h at rt, poured into brine and extracted with Et_2O. Drying, filtering and concentration gave a crude residue that was flash cromatographed on silica gel (2-3 % EtOAc/hexanes), affording 176 mg of **2b** [49%, R_f= 0.18 (6% EtOAc/hexanes), colorless oil], and 87 mg of **3b** [24% R_f= 0.28 (6% EtOAc/hexanes), colorless oil].

The use of allyllithium (6.25 mL, 2.2 mmol, 0.35 M in THF) instead of vinyllithium, afforded 314 mg of a chromatographically unseparable mixture of compounds **7** and **8** [81%, R_f= 0.38 (6% EtOAc/hexanes), colorless oil]. Ratio 2: 1 determined by ^{1}H NMR integration of characteristic alkenyl hydrogens.

Compound **2b**

^{1}H NMR δ (ppm): 6.19 (1H, dd, *J* = 10.8, 17.4 Hz), 5.78-5.44 (1H, m), 5.4 (1H, dd, *J* = 17.6, 0.9 Hz), 5.3 (1H, dd, *J* = 10.6, 0.7 Hz), 5.0 (2H, m), 2.97 (1H, m), 2.54-2.36 (1H, m), 2.12-1.83 (5H, m), 1.8-1.65 (1H, m), 1.55-1.41 (1H, m).

^{13}C NMR δ (ppm): 212.4 (C), 138.9 (CH), 135.9 (CH), 116.6 (CH_2), 114.7 (CH_2), 78.4 (C), 46.6 (CH), 40.0 (CH_2), 34.2 (CH_2), 32.7 (CH_2), 19.6 (CH_2).

LRMS (*m/z*) : 180 (M^+, 2), 169 (18), 149 (31), 96 (19), 95 (17), 83 (33), 79 (22).

HRMS calcd. for $C_{11}H_{16}O_2$ 180.1150, found 180.1150.

Compound **3b**

^{1}H NMR δ (ppm): 6.16 (1H, dd, *J* = 17.1, 10.5 Hz), 5.74 (1H, m), 5.45 (1H, d, *J* = 17.1 Hz), 5.26 (1H, d, *J* = 10.5 Hz), 5.02 (2H, m), 4.23 (1H, s), 2.68-2.53 (2H, m), 2.32-2.16 (2H, m), 2.03 (1H, m), 1.86-1.68 (3H, m), 1.38-1.32 (1H, m).

^{13}C NMR δ (ppm): 211.9 (C), 137.2 (CH), 135.7 (CH), 116.7 (CH_2), 116.65 (CH_2), 79.4 (C), 46.7 (CH), 41.8 (CH_2), 34.1 (CH_2), 33.3 (CH_2), 21.8 (CH_2).

LRMS (*m/z*): 170 (14), 169 (100), 149 (23), 111 (16), 96 (22), 83 (36).

HRMS calcd. for $C_{11}H_{16}O_2$ 180.1150, found 180.1153.

Compound **2a**

^{1}H NMR δ (ppm): 6.12-6.28 (1H, m), 5.72 (1H, m), 5.21 (2H, m), 4.88 (2H, m), 3.0 (1H, m), 2.46 (1H, m), 2.18-1.74 (4H, m), 1.69-1.46 (2H, m), 0.62 (1H, m), 0.31 (9H, s), 0.02 (3H, s), -0.08 (3H, s).

^{13}C NMR δ (ppm): 211.6 (C), 139.1 (CH), 136.5 (CH), 116.3 (CH_2), 115.9 (CH_2), 79.0 (C), 45.5 (CH), 38.1 (CH_2), 34.4 (CH_2), 33.5 (CH_2), 25.6 (CH_3), 20.3 (CH_2), 18.6 (C), -2.2 (CH_3), -2.6 (CH_3).

Compound **3a**

^1H NMR δ (ppm): 6.10 (1H, dd, *J*= 17.1, 10.5 Hz), 5.76 (1H, m), 5.35 (1H, dd, *J* = 17.1, 1.2 Hz), 5.24 (1H, dd, *J* = 10.5, 1.2 Hz), 5.01 (2H, m), 2.54 (2H, m), 2.21-1.96 (3H, m), 1.77 (3H, m), 1.26 (1H, m), 0.88 (9H, s), 0.15 (3H, s), 0.07 (3H, s).

^{13}C NMR δ (ppm): 209.6 (C), 138.9 (CH), 136.3 (CH), 116.8 (CH_2), 116.3 (CH_2), 82.9 (C), 47.9 (CH), 42.9 (CH_2), 33.6 (CH_2), 33.5 (CH_2), 26.0 (CH_3), 22.3 (CH_2), 18.6 (C), -2.3 (CH_3), -2.4 (CH_3).

LMRS (*m/z*): 294 (M^+, 0.04), 237 [M^+-$C(CH_3)_3$, 4], 167 (26), 149 (100), 112 (11).

Procedure for the RCM

Catalyst **4** (30 mg, 0.036 mmol) was added to a mixture of **2b** (96 mg, 0.533 mmol) and **3b** (48 mg, 0.266 mmol) in CH_2Cl_2 (160 mL). The reaction mixture was stirred at rt for 9 h, the solvent evaporated, and the residue purified by flash cromatography on silica gel (5-10% EtOAc/hexanes) to afford 77 mg of **5b** as a white solid [63% (95 % based on **2b**), R_f= 0.32 (25 % EtOAc/hexanes), mp= 82°C] and 46 mg of unreacted **3b**.

The same procedure was used for the cyclization of a mixture of **7** and **8** (115 mg of a 2:1 mixture, 0.593 mmol). In this case, 20 mg of catalyst **4** (0.024 mmol) were used, and completion of the reaction required 15 h at rt. After the corresponding chromatography 57 mg of **9** were obtained as a white solid [58% (87% based on **7**), R_f= 0.38 (15% EtOAc/hexanes), mp= 89°C]. A high proportion of unreacted **8** was recovered (34 mg).

Compound **5b**

^1H NMR δ (ppm): 5.85 (1H, m), 5.52 (1H, m), 3.79 (1H, br s), 2.87-2.67 (2H, m), 2.45-2.37 (1H, m), 2.05 (1H, m), 1.99-1.60 (5H, m).

^{13}C NMR δ (ppm): 213.9 (C), 131.7 (CH), 129.0 (CH), 76.0 (C), 44.7 (CH), 41.2 (CH_2), 36.7 (CH_2), 36.1 (CH_2), 19.4 (CH_2).

LMRS (*m/z*): 152 (M^+, 3), 149 (100), 95 (27), 85 (15), 69 (23).

HRMS calcd. for $C_9H_{12}O_2$ 152.0837, found 152.0831.

Compound **9** :

^1H NMR δ (ppm): 5.86-5.78 (2H, m), 4.21 (1H, br s), 2.95 (1H, m), 2.69 (1H, m), 2.41-2.14 (5H, m), 1.97-1.74 (3H, m), 1.56 (1H, m).

^{13}C NMR δ (ppm): 216.3 (C), 129.8 (CH), 127.4 (CH), 78.7 (C), 46.6 (CH), 42.3 (CH_2), 39.5 (CH_2), 33.6 (CH_2), 30.1 (CH_2), 20.9 (CH_2).

LRMS (*m/z*): 167 (M^++1, 27), 149 (M^+-17, 100), 112 (39), 104 (24), 84 (35), 83 (30).

HR-FABMS+ calcd. for $C_{10}H_{15}O_2$ 167.1072, found 167.1070.

Compound **8** :

^{1}H NMR δ (ppm): 5.79-5.55 (2H, m), 5.04-4.89 (4H, m), 4.03 (1H, br s), 2.6-2.34 (4H, m), 2.23-2.08 (2H, m), 2.02-1.85 (1H, m), 1.76-1.47 (3H, m), 1.36-1.18 (1H, m).

^{13}C NMR δ (ppm): 213.7 (C), 136.8 (CH), 135.2 (CH), 120.5 (CH_2), 116.7 (CH_2), 77.6 (C), 46.5 (CH), 41.9 (CH_2), 40.6 (CH_2), 34.4 (CH_2), 34.0 (CH_2), 20.72(CH_2).

HR-FABMS+ calcd. for $C_{12}H_{19}O_2$ 195.1385, found 195.1385.

Fragmentation reaction

$Pb(OAc)_4$ (300 mg, 0.676 mmol) was added to a solution of **5b** (63 mg, 0.379 mmol) in MeOH (12 mL). The reaction was stirred at rt for 5 min, poured into brine and extracted with Et_2O. Drying, filtering and concentration gave a crude that was purified by flash cromatography on silica gel (7% EtOAc/hexanes) to afford 63 mg of cyclooctenone **6** as a colorless oil [84%, R_f= 0.34 (15% EtOAc/hexanes)]

Similar treatment of compound **9** led to 61 mg of cyclononene **10** [78%, R_f= 0.34 (15% EtOAc/hexanes), colorless oil].

Compound **6**

^{1}H NMR δ (ppm): 6.42 (1H, dt, *J* = 12.3, 7.9 Hz), 6.14 (1H, d, *J* = 12.3 Hz), 3.67 (3H, s), 2.89-2.63 (5H, m), 1.94-1.70 (4H, m).

^{13}C NMR δ (ppm): 203.3 (C), 175.0 (C), 139.9 (CH), 135.1 (CH), 51.9 (CH_3), 41.9 (CH_2), 40.3 (CH), 29.2 (CH_2), 26.6 (CH_2), 20.9 (CH_2).

LRMS (*m/z*): 182 (M^+, 3), 150 (20), 149 (29), 123 (M^+- CO_2CH_3, 41), 97 (26), 95 (100), 81 (72), 79 (53).

HR-FABMS+ calcd. for $C_{10}H_{15}O_3$ 183.1017, found 183.1021.

Compound **10**:

^{1}H NMR δ (ppm): 5.71-5.50 (2H, m), 3.65 (3H, s), 3.26 (1H, m), 3.01 (1H, m), 2.59-2.31 (5H, m), 1.83-1.55 (4H, m).

^{13}C NMR δ (ppm): 211.9 (C), 175.6 (C), 130.4 (CH), 124.7 (CH), 52.1 (CH_3), 44.7 (CH_2), 42.4 (CH), 41.6 (CH_2), 27.1 (CH_2), 26.9 (CH_2), 20.4 (CH_2).

LRMS (*m/z*): 149 (8), 114 (20), 85 (12), 71 (26), 58 (100).

HR-FABMS+ calcd. for $C_{11}H_{17}O_3$ 197.1177, found 197.1168.