

New Synthetic Technology for the Mild and Selective One-Carbon Homologation of Hindered Aldehydes in the Presence of Ketones

K. C. Nicolaou*, Georgios Vassilikogiannakis, Remo Kranich, Phil S. Baran, Yong-Li Zhong, and Swaminathan Natarajan

Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037 and Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093
kcn@scripps.edu

Supporting Information Available

(Entry 2, Table 1) R_f = 0.46 (silica gel, hexane/EtOAc 3:1); IR (film) $\nu_{\max}$ (cm^{-1}) = 2929 s, 2854 m, 2243 w ($\text{C}\equiv\text{N}$), 1610 m, 1574 w, 1501 s, 1463 m, 1420 w, 1381 w, 1344 w, 1283 m, 1248 m, 1218 w, 1121 w, 1071 w, 1043 m, 977 w, 920 w, 869 w, 847 w, 805 w, 731 w, 710 w, 651 w, 603 w; ^1H NMR (500 MHz, CDCl_3): δ = 1.18 (s, 3 H), 1.21 (s, 3 H), 1.27 (tdd, J_1 = 13.6 Hz, J_2 = 4.0 Hz, J_3 = 1.1 Hz, 1 H), 1.45 (td, J_1 = 12.8 Hz, J_2 = 4.0 Hz, 1 H), 1.53 (dd, J_1 = 12.8 Hz, J_2 = 2.2 Hz, 1 H), 1.59-1.76 (m, 3 H), 1.89-1.96 (m, 2 H), 2.30 (bd, J = 12.8 Hz, 1 H), 2.35 (dd, J_1 = 16.5 Hz, J_2 = 1.5 Hz, 1 H), 2.66 (d, J = 16.9 Hz, 1 H), 2.76-2.85 (m, 1 H), 2.91 (dd, J_1 = 15.8 Hz, J_2 = 7.0 Hz, 1 H), 3.77 (s, 3 H), 6.68 (dd, J_1 = 8.4 Hz, J_2 = 2.9 Hz, 1 H), 6.78 (d, J = 8.4 Hz, 1 H), 6.96 (d, J = 8.4 Hz, 1 H); ^{13}C NMR (125 MHz, CDCl_3): δ = 18.7, 18.9, 23.1, 24.8, 29.4, 29.5, 35.6, 37.7, 38.1, 38.2, 50.1, 55.2, 110.1, 111.1, 118.8, 126.6, 129.8, 150.2, 157.8; HRMS (MALDI) calcd for $\text{C}_{19}\text{H}_{26}\text{NO}$ [$\text{M} + \text{H}^+$] 284.2009, found: 284.2015.

2

(Entry 3, Table 1) $R_f = 0.22$ (silica gel, hexane/EtOAc 1:1); IR (film) $\nu_{\max}$ (cm^{-1}) = 2989 m, 2951 m, 2255 w ($\text{C}\equiv\text{N}$), 1711 s, 1670 s, 1380 m, 1204 s, 1041 m; ^1H NMR (500 MHz, CDCl_3): δ = 5.19 (dd, $J_1 = 5.5$ Hz, $J_2 = 1.1$ Hz, 1 H), 5.16 (d, $J = 1.1$ Hz, 1 H), 4.78 (dd, $J_1 = 5.5$ Hz, $J_2 = 4.0$ Hz, 1 H), 4.71 (m, 1 H), 3.69 (s, 3 H), 2.99 (m, 2 H), 1.47 (s, 3 H), 1.43 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3): δ = 167.5, 165.4, 115.5, 114.9, 93.3, 81.5, 80.1, 76.5, 51.1, 26.9, 26.0, 18.3; HRMS (MALDI): calcd for $\text{C}_{12}\text{H}_{15}\text{NO}_5\text{Na}$ [$\text{M} + \text{Na}^+$] 276.0842, found: 276.0851.

(Entry 4, Table 1) $R_f = 0.25$ (silica gel, hexane/EtOAc 1:1); IR (film) $\nu_{\max}$ (cm^{-1}) = 2988 m, 2951 m, 2254 w ($\text{C}\equiv\text{N}$), 1712 s, 1662 s, 1380 s, 1212 m, 1124 s, 1046 m; ^1H NMR (500 MHz, CDCl_3): δ = 5.81 (dd, $J_1 = 6.2$ Hz, $J_2 = 1.4$ Hz, 1 H), 5.50 (d, $J = 0.8$ Hz, 1 H), 4.82 (dd, $J_1 = 6.2$ Hz, $J_2 = 4.4$ Hz, 1 H), 4.46 (m, 1 H), 3.72 (s, 3 H), 2.86 (d, $J = 6.6$ Hz, 2 H), 1.46 (s, 3 H), 1.43 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3): δ = 170.2, 166.8, 116.0, 114.0, 95.6, 79.6, 78.7, 77.2, 51.3, 26.3, 25.3, 18.5; HRMS (MALDI): calcd for $\text{C}_{12}\text{H}_{15}\text{NO}_5\text{Na}$ [$\text{M} + \text{Na}^+$] 276.0842, found: 276.0852.

(Entry 5, Table 1) $R_f = 0.50$ (silica gel, hexane/EtOAc 2:1); IR (film) $\nu_{\max}$ (cm^{-1}) = 2953 s, 2929 s, 2244 w ($\text{C}\equiv\text{N}$), 1710 m, 1462 m, 1385 m, 1252 m, 1091 s, 836 m, 773 m; ^1H NMR (600 MHz, CDCl_3): δ = 2.97 (d, $J = 3.5$ Hz, 1 H), 2.62 (dd, $J_1 = 14.9$ Hz, $J_2 = 4.8$ Hz, 1 H), 2.45 (m, 1 H), 2.27 (dd, $J_1 = 14.9$ Hz, $J_2 = 11.9$ Hz, 1 H), 1.72 (m, 1 H), 1.60 (m, 2 H), 1.49 (m, 1 H), 1.32 (m, 2 H), 1.24 (m, 1 H), 1.06 (s, 3 H), 0.86 (s, 9 H), 0.81 (s, 3 H), 0.76 (s, 3 H), 0.01 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (150 MHz, CDCl_3): δ = 178.8, 85.6, 49.9, 47.7, 47.6, 34.0, 27.8, 26.9, 25.7, 20.9, 20.0, 19.5, 17.8, 13.6, 12.3, -4.0, -4.6.

(Entry 6, Table 1) $R_f = 0.62$ (silica gel, hexane/ Et_2O 3:1); IR (film) $\nu_{\max}$ (cm^{-1}) = 2917 s, 2858 m, 2247 w ($\text{C}\equiv\text{N}$), 1459 m, 1424 w, 1389 w, 1365 w; ^1H NMR (400 MHz, CDCl_3): δ = 2.34 (q, $J = 7.3$ Hz, 1 H), 2.21 (t, $J = 6.4$ Hz, 2 H), 2.10 (dd, $J_1 = 11.2$ Hz, $J_2 = 5.9$ Hz, 1 H), 1.72-1.94 (m, 5 H), 1.25-1.36 (m, 2 H), 1.23 (s, 3 H), 0.84 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ = 119.3, 44.9, 40.3, 39.5, 32.4, 26.4, 23.8, 23.4, 22.9, 21.6, 19.8.

3

(Entry 7, Table 1) $R_f = 0.24$ (silica gel, hexane/EtOAc 3:1); IR (film) $\nu_{\max}$ (cm^{-1}) = 2988 m, 2936 m, 2254 w ($\text{C}\equiv\text{N}$), 1458 w, 1417 w, 1381 m, 1308 w, 1256 m, 1213 s, 1169 m, 1142 w, 1103 m, 1071 s, 1006 s, 942 w, 917 w, 890 m, 861 w, 803 w, 766 w, 688 w, 650 w, 624 w; ^1H NMR (500 MHz, CDCl_3): δ = 1.32 (s, 3 H), 1.34 (s, 3 H), 1.43 (s, 3 H), 1.52 (s, 3 H), 2.63 (dd, $J_1 = 16.5$ Hz, $J_2 = 6.6$ Hz, 1 H), 2.68 (dd, $J_1 = 16.5$ Hz, $J_2 = 7.3$ Hz, 1 H), 4.04 (td, $J_1 = 7.0$ Hz, $J_2 = 1.8$ Hz, 1 H), 4.22 (dd, $J_1 = 7.7$ Hz, $J_2 = 1.8$ Hz, 1 H), 4.32 (dd, $J_1 = 5.1$ Hz, $J_2 = 2.6$ Hz, 1 H), 4.64 (dd, $J_1 = 7.7$ Hz, $J_2 = 2.6$ Hz, 1 H), 5.48 (d, $J = 5.1$ Hz, 1 H); ^{13}C NMR (125 MHz, CDCl_3): δ = 19.3, 24.4, 24.8, 25.8, 26.0, 64.3, 70.2, 70.7, 71.1, 96.3, 109.0, 109.8, 117.0; HRMS (MALDI) calcd for $\text{C}_{13}\text{H}_{19}\text{NO}_5\text{Na}$ [$\text{M} + \text{Na}^+$] 292.1155, found: 292.1153.

(Entry 4, Table 2) $R_f = 0.39$ (silica gel, hexane/EtOAc 4:1); IR (film) $\nu_{\max}$ (cm^{-1}) = 3079 w, 2993 m, 2945 s, 2874 m, 2240 w ($\text{C}\equiv\text{N}$), 1700 s, 1648 w, 1458 s, 1373 m, 1312 w, 1227 m, 1180 m, 911 m, 880 m, 734 m; ^1H NMR (400 MHz, CDCl_3): δ = 4.67 (d, $J = 1.8$ Hz, 1 H), 4.59 (t, $J = 1.8$ Hz, 1 H), 2.53 (dd, $J_1 = 16.7$ Hz, $J_2 = 2.1$ Hz, 1 H), 2.35-2.49 (m, 2 H), 2.28 (m, 1 H), 2.09 (dd, $J_1 = 16.7$ Hz, $J_2 = 1.2$ Hz, 1 H), 1.81-1.99 (m, 4 H), 1.66 (brs, 3 H), 1.55-1.64 (m, 2 H), 1.34-1.54 (m, 11 H), 1.07-1.33 (m, 5 H), 1.05 (s, 3 H), 1.03 (s, 3 H), 1.00 (s, 3 H), 0.96 (s, 3 H), 0.91 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ = 217.8, 148.9, 119.0, 110.4, 68.1, 54.7, 49.5, 47.8, 47.2, 47.1, 45.9, 42.6, 40.6, 39.4, 37.9, 36.7, 36.4, 34.0, 33.3, 31.4, 29.0, 26.8, 26.5, 24.8, 21.1, 20.9, 19.5, 19.0, 15.9, 15.7, 14.6.

(Entry 5, Table 2) $R_f = 0.40$ (silica gel, hexane/EtOAc 1:1); IR (film) $\nu_{\max}$ (cm^{-1}) = 2961 s, 2245 w ($\text{C}\equiv\text{N}$), 1737 s ($\text{C}=\text{O}$), 1453 m, 1374 m, 1046 w; ^1H NMR (500 MHz, CDCl_3): δ = 2.53 (dt, $J_1 = 7.3$ Hz, $J_2 = 1.4$ Hz, 2 H), 2.44 (m, 1 H), 2.11 (t, $J = 4.4$ Hz, 1 H), 2.00 (m, 1 H), 1.82 (m, 1 H), 1.63 (m, 2 H), 1.45 (m, 1 H), 1.28 (m, 1 H), 1.00 (s, 3 H), 0.89 (s, 3 H), 0.88 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3): δ = 219.9, 119.2, 48.0, 46.2, 45.9, 30.9, 25.1, 23.6, 20.1, 19.4, 19.0, 16.0, 9.4; ESIMS ($\text{C}_{13}\text{H}_{19}\text{NO}$): m/z (%) 205 ($[\text{M}]^+$, 50).

4

(Entry 6, Table 2) $R_f = 0.10$ (silica gel, hexane/EtOAc 1:1); IR (film) $\nu_{\max}$ (cm^{-1}) = 2940 s, 2869 s, 2245 w ($\text{C}\equiv\text{N}$), 1668 s, 1615 m, 1454 br m, 1231 m, 916 m, 732 s; ^1H NMR (500 MHz, CDCl_3): δ = 5.68 (s, 1 H), 2.17-2.43 (m, 6 H), 1.98 (m, 2 H), 1.81 (m, 3 H), 1.65 (m, 2 H), 1.51 (m, 2 H), 1.18-1.45 (m, 5 H), 1.15 (s, 3 H), 1.13 (d, $J = 6.6$ Hz, 3 H), 0.87-1.10 (m, 3 H), 0.70 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3): δ = 199.2, 171.0, 123.7, 118.7, 55.5, 54.6, 53.4, 42.3, 39.1, 38.4, 35.5, 35.4, 33.8, 33.4, 32.6, 31.7, 27.8, 24.6, 23.9, 20.8, 19.1, 17.2, 11.9; HRMS (MALDI) calcd for $\text{C}_{23}\text{H}_{34}\text{NO}_5$ [$\text{M} + \text{H}^+$] 340.2635, found: 340.2620.

(Entry 7, Table 2) R_f 0.19 (silica gel, EtOAc/hexane 3:4); IR (film) $\nu_{\max}$ (cm^{-1}) 3070 w, 2957 s, 2931 s, 2857 m, 2250 w ($\text{C}\equiv\text{N}$), 1710 s ($\text{C}=\text{O}$), 1588 w, 1469 m, 1443 m, 1427 m, 1394 w, 1307 s, 1146 s, 1109 s, 1080 s, 1022 w, 976 w, 912 m, 822 w, 802 w, 734 s, 705 s, 614 w; ^1H NMR (500 MHz, CDCl_3) δ 1.02 (s, 9 H), 1.17 (s, 3 H), 1.27 (s, 3 H), 1.50-1.67 (m, 3 H), 1.68-1.75 (m, 1 H), 1.99 (dd, $J_1 = 14.7$ Hz, $J_2 = 1.8$ Hz, 1 H), 2.10 (d, $J = 16.5$ Hz, 1 H), 2.24 (ddd, $J_1 = 15.0$ Hz, $J_2 = 12.5$ Hz, $J_3 = 4.8$ Hz, 1 H), 2.35-2.47 (m, 2 H), 2.51-2.60 (m, 1 H), 2.70 (d, $J = 16.9$ Hz, 1 H), 3.39 (s, 1 H), 3.43 (dd, $J_1 = 14.7$ Hz, $J_2 = 4.0$ Hz, 1 H), 3.52-3.60 (m, 2 H), 3.62-3.67 (m, 1 H), 4.47 (dd, $J_1 = 7.0$ Hz, $J_2 = 4.0$ Hz, 1 H), 7.36-7.47 (m, 8 H), 7.48-7.53 (m, 1 H), 7.62-7.68 (m, 4 H), 7.86-7.90 (m, 2 H); ^{13}C NMR (125 MHz, CDCl_3) δ 19.1, 26.6, 26.8, 27.5, 28.0, 28.8, 35.8, 36.3, 36.8, 38.2, 40.4, 43.6, 49.7, 60.6, 63.4, 71.9, 76.2, 118.7, 127.65, 127.7, 128.1, 129.2, 129.6, 133.4, 133.5, 133.9, 135.55, 135.6, 139.1, 210.3; HRMS (MALDI) calcd for $\text{C}_{39}\text{H}_{47}\text{NO}_5\text{SSiNa}$ [$\text{M} + \text{Na}^+$] 692.2858, found: 692.2865.