Double Deprotonation of Acetylenic Oxiranes: Synthesis of Allenic Ketones through Dilithio Ynenolates

Aurélien Denichoux, Franck Ferreira and Fabrice Chemla

General Remarks: Experiments involving organometallics were carried out in dried glassware under a positive pressure of dry nitrogen. Liquid nitrogen was used as a cryoscopic fluid. A four necked round bottom flask equipped with an internal thermometer, a septum cap, a nitrogen or argon inlet and a mechanic stirring was used. THF was freshly distilled from sodium benzophenone ketyl prior to use. Commercial *n*-BuLi and *t*-BuLi was titrated with an 1 M solution of *s*-BuOH in toluene in the presence of 2,2'-diquinoline. All other reagents and solvents were of commercial quality and were used without purification. Flash column chromatographic separations were carried out over Merck silica gel 60 (0.015–0.040 mm). ¹H NMR and ¹³C NMR spectra were recorded on a Bruker AVANCE 400 spectrometer at 400 MHz and 100 MHz respectively. Chemical shifts are reported in ppm relative to an internal standard of residual chloroform (7.26 ppm for ¹H NMR and 77.16 ppm for ¹³C NMR) unless otherwise noted. IR spectra were recorded with a ATRD Bruker Tensor 27 spectrophotometer. Melting points were not corrected and were measured with a Stuart Scientific Melting Point Apparatus SMP3 (1° C). Elemental analyses were performed by the Service de Microanalyse de l'Université Pierre et Marie Curie (Paris).

General procedure: To a solution of epoxide (0.5 mmol) in THF (5 mL) was added RLi (2 or 3 mmol) at –80°C. After 10 min stirring, the mixture was allowed to warm to –20°C and the progress of the reaction was monitored by GC. After completion of the reaction, the mixture was hydrolysed with 0.5 M HCl and diluted with Et₂O. The layers were separated, and the aqueous one was extracted twice with Et₂O. The combined organic phases were washed with water then brine, dried over anhydrous MgSO₄ (for **2a-d, f**) or Na₂SO₄ (for **2e, g-i**). The volatiles were removed in vacuo to give the corresponding allenic ketones which could be purified for analytical purposes.

1-Cyclohexylbuta-2,3-dien-1-one (2a): From **1a** (75 mg, 0.50 mmol) and *n*-BuLi (1.10 mmol, 2.2 M in hexanes) was obtained **2a** (65 mg, 0.43 mmol, 87%) as a brown oil. For analytical purposes, the residue was purified by column chromatography on silica gel (eluent : 8% Et₂O in pentane) to afford **2a** (45 mg, 0.30 mmol, 60%) as a pale yellow oil. ¹H NMR (CDCl₃, 400 MHz) : δ = 5.73 (t, 1H, *J* = 6.6 Hz), 5.21 (d, 2H, *J* = 6.6 Hz), 2.86-2.80 (m, 1H), 1.78-1.75 (m, 4H), 1.68-1.60 (m, 1H), 1.41-1.12 (m, 5H); ¹³C NMR (CDCl₃, 100 MHz) : δ = 216.3, 204.1, 95.6, 79.3, 47.2, 29.3, 25.9, 25.7; IR : 2928, 2853, 1959, 1932, 1672, 1163, 845, 624 cm⁻¹

1-Cyclohexylbuta-3,3-dideuterio-2,3-dien-1-one (D₂-2a): To a solution of **1a** (80 mg, 0.53 mmol) in THF (5 mL) was added *n*-BuLi (1.17 mmol, 2.2 M in hexanes) at –80°C. After 10 min stirring, the mixture was allowed to warm to –20°C and the progress of the reaction was

monitored by GC. After completion of the reaction, the mixture was hydrolysed with D₂O and diluted with Et₂O. The layers were separated, and the aqueous one was extracted twice with Et₂O. The combined organic phases were washed with water then brine, dried over anhydrous MgSO₄. Evaporation of the solvent and chromatography on silica gel (eluent : 4% Et₂O in pentane) afforded **D₂-2a** (47 mg, 0.31 mmol, 58%) as a pale yellow oil. ¹H NMR (CDCl₃, 400 MHz) : = 5.74 (s, 1H), 2.90-2.79 (m, 1H), 1.79-1.76 (m, 4H), 1.70-1.62 (m, 1H), 1.42-1.15 (m, 5H); ¹³C NMR (CDCl₃, 100 MHz) : = 216.5, 204.1, 95.8, 79.3, 47.2, 29.3, 26.0, 25.8; IR : 2928, 2854, 2208, 1919, 1671, 1449, 1166, 1116, 841, 673, 623 cm⁻¹

1-Cyclohexylbuta-2-deuterio-2,3-dien-1-one (D-2a): From **D-1a** (74 mg, 0.49 mmol) and *n*-BuLi (1.08 mmol, 2.20 M in hexanes) was obtained **D-2a** (63 mg, 0.42 mmol, 85%) as a brown oil. For analytical purposes, the residue was purified by column chromatography on silica gel (eluent : 8% Et₂O in pentane) to afford **D-2a** (48 mg, 0.32 mmol, 64%) as a pale yellow oil. ¹H NMR (CDCl₃, 400 MHz) : = 5.22 (s, 2H), 2.90-2.80 (m, 1H), 1.79-1.76 (m, 4H), 1.70-1.61 (m, 1H), 1.42-1.15 (m, 5H); ¹³C NMR (CDCl₃, 100 MHz) : = 216.4, 204.1, 95.4 (q), 79.4, 47.2, 29.3, 26.0, 25.8; IR : 2928, 2853, 1925, 1667, 1149, 1114, 894, 844, 602 cm⁻¹

5-Methylhepta-1,2-dien-4-one (2b): From **1b** (124 mg, 1.00 mmol) and *n*-BuLi (2.20 mmol, 2.20 M in hexanes) was obtained **2b** (82 mg, 0.66 mmol, 66%) as a brown oil. For analytical purposes, the residue was purified by column chromatography on silica gel (eluent : 8% Et₂O in pentane) to afford **2b** (25 mg, 0.20 mmol, 20%) as a colourless oil. ¹H NMR (CDCl₃, 400 MHz) : = 5.78 (t, 1H, *J* = 6.4 Hz), 5.22 (d, 2H, *J* = 6.4 Hz), 2.98 (sext, 1H, *J* = 6.8 Hz), 1.72-1.60 (m, 1H), 1.43-1.30 (m, 1H), 1.06 (d, 3H, *J* = 6.8 Hz), 0.87 (t, 3H, *J* = 7.3 Hz); ¹³C NMR (CDCl₃, 100 MHz) : = 216.7, 204.9, 96.3, 79.4, 43.8, 26.9, 16.8, 11.8; IR : 2966, 2934, 2877, 1958, 1933, 1674, 1181, 1141, 873, 846, 630 cm⁻¹

5-Ethylhepta-1,2-dien-4-one (2c): From **1c** (71 mg, 0.51 mmol) and *n*-BuLi (1.12 mmol, 2.20 M in hexanes) was obtained **2c** (61 mg, 0.44 mmol, 86%) as a brown oil. For analytical purposes, the residue was purified by column chromatography on silica gel (eluent : 2% Et₂O in pentane) to afford **2c** (45 mg, 0.33 mmol, 64%) as a colourless oil. ¹H NMR (CDCl₃, 400 MHz) : = 5.82 (t, 1H, *J* = 6.3 Hz), 5.23 (d, 2H, *J* = 6.3 Hz), 2.92-2.82 (m, 1H), 1.68-1.57 (m, 2H), 1.50-1.38 (m, 2H), 0.85 (t, 6H, *J* = 7.4 Hz); ¹³C NMR (CDCl₃, 100 MHz) : = 217.1, 204.9, 97.6, 79.5, 50.9, 25.2, 11.9; IR : 2963, 2932, 2876, 1958, 1932, 1672, 1459, 1174, 1138, 873, 845, 627 cm⁻¹

1-Phenylhexa-4,5-dien-3-one (2d): From **1d** (172 mg, 1.00 mmol) and *n*-BuLi (2.20 mmol, 2.20 M in hexanes) was obtained **2d** (139 mg, 0.81 mmol, 81%) as a brown oil. For analytical purposes, the residue was purified by column chromatography on silica gel (eluent : 10% Et₂O in pentane) to afford **2d** (99 mg, 0.58 mmol, 58%) as a colourless oil. ¹H NMR (CDCl₃, 400 MHz) : = 7.30-7.27 (m, 2H), 7.22-7.18 (m, 3H), 5.79 (t, 1H, *J* = 6.6 Hz), 5.20 (d, 2H, *J* = 6.6 Hz), 2.93 (s, 4H); ¹³C NMR (CDCl₃, 100 MHz) : = 216.9, 199.9, 141.2, 128.6, 128.5, 126.2, 96.8, 79.7, 41.0, 30.5; IR : 3063-2928, 1957, 1930, 1677, 1203, 849, 748, 698 cm⁻¹; Anal. Calcd for C₁₂H₁₂O : C, 83.69 ; H, 7.02. Found C, 83.52 ; H, 7.19.

1-Phenylbuta-2,3-dien-1-one (2e): From **1e** (77 mg, 0.53 mmol) and *t*-BuLi (1.44 mmol, 1.60 M in pentane) was obtained **2e** (50 mg, 0.35 mmol, 65%) as a brown oil. For analytical purposes, the residue was purified by column chromatography on silica gel (eluent : 5% Et₂O in pentane) to afford **2e** (40 mg, 0.28 mmol, 51%) as a yellow oil. ¹H NMR (CDCl₃, 400 MHz) : δ = 7.90 (d, 2H, *J* = 7.4 Hz), 7.56 (t, 1H, *J* = 7.4 Hz), 7.45 (t, 2H, *J* = 7.4 Hz), 6.47 (t, 1H, *J* = 6.6 Hz), 5.26 (d, 2H, *J* = 6.6 Hz); ¹³C NMR (CDCl₃, 100 MHz) : δ = 217.2, 191.2, 137.5, 132.9, 128.8, 128.5, 93.3, 79.4; IR : 3062, 2987, 1959, 1931, 1647, 1596, 1577, 1275, 1213, 977, 712, 688, 670, 631 cm⁻¹

1,2-Diphenylbuta-2,3-dien-1-one (2f): From **1f** (110 mg, 0.50 mmol) and *n*-BuLi (1.50 mmol, 2.20 M in hexanes) was obtained **2f** (99 mg, 0.45 mmol, 90%) as a brown oil. For analytical purposes, the residue was purified by column chromatography on silica gel (eluent : 4% Et₂O in pentane) to afford **2f** (64 mg, 0.29 mmol, 58%) as a white solid. ¹H NMR (CDCl₃, 400 MHz) : δ = 7.96-7.93 (m, 2H), 7.60-7.52 (m, 1H), 7.48-7.43 (m, 4H), 7.40-7.36 (m, 2H), 7.32-7.27 (m, 1H), 5.36 (s, 2H); ¹³C NMR (CDCl₃, 100 MHz) : δ = 214.8, 193.5, 138.1, 133.1, 132.8, 129.7, 128.7, 128.4, 128.1, 127.9, 108.7, 81.6; IR : 3051, 2976, 1943, 1911, 1646, 1445, 1284, 1245, 1077, 1050, 1020, 919, 799, 762, 729, 695, 639 cm⁻¹; Mp : 69°C; Anal. Calcd for C₁₂H₁₂O : C, 87.25 ; H, 5.49. Found C, 87.03 ; H, 5.71.

3-Pentylnona-1,2-dien-4-one (2g): From **1g** (107 mg, 0.51 mmol) and *t*-BuLi (1.13 mmol, 1.60 M in pentane) was obtained **2g** (70 mg, 0.34 mmol, 44%) as a brown oil. For analytical purposes, the residue was purified by column chromatography on silica gel (eluent : 2% Et₂O in pentane) to afford **2g** (19 mg, 0.09 mmol, 18%) as a pale yellow oil. ¹H NMR (CDCl₃, 400 MHz) : δ = 5.16 (t, 2H, *J* = 2.9 Hz), 2.63 (t, 2H, *J* = 7.6 Hz), 2.18-2.13 (m, 2H), 1.61-1.54 (m, 2H), 1.40-1.28 (m, 10H), 0.95-0.80 (m, 6H); ¹³C NMR (CDCl₃, 100 MHz) : δ = 216.4, 201.7, 108.7, 79.6, 39.4, 31.6, 31.57, 27.7, 26.4, 24.9, 22.6, 14.2, 14.1; IR : 2956, 2928, 2860, 1934, 1678, 1465, 1174, 842 cm⁻¹

3-Phenylpenta-3,4-dien-2-one (2h) and 2-Methyl-1-phenylbuta-2,3-dien-1-one (2i):

From (*R**,*R**)-**1h** (77 mg, 0.49 mmol) and *t*-BuLi (1.07 mmol, 1.60 M in pentane) was obtained a mixture of **2h** and **2i** (**2h/2i** : 69/31). The residue was purified by column chromatography on silica gel (eluent : 2% Et₂O in pentane) to afford **2i** (6 mg, 0.04 mmol, 8%) and **2h** (15 mg, 0.09 mmol, 19%) as a pale yellow oil.

From a mixture of (*R**,*S**)-**1h** and (*R**,*R**)-**1h** (*cis/trans* : 96/4, 78 mg, 0.49 mmol) and *t*-BuLi (1.08 mmol, 1.60 M in pentane) was obtained a mixture of **2h** and **2i** (**2h/2i** : 91/9). The residue was purified by column chromatography on silica gel (eluent : 2% Et₂O in pentane) to afford **2i** (4 mg, 0.03 mmol, 5%) and **2h** (34 mg, 0.22 mmol, 43%) as a pale yellow oil.

For **2h**: ¹H NMR (CDCl₃, 400 MHz) : δ = 7.42-7.4 (m, 2H), 7.37-7.33 (m, 2H), 7.30-7.23 (m, 1H), 5.46 (s, 2H), 2.47 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) : δ = 218.3, 197.2, 131.8, 129.1, 128.4, 127.9, 110.9, 80.5, 28.2; IR : 3057, 2955, 2869, 1949, 1921, 1681, 1232, 894, 851, 761, 696, 648, 592 cm⁻¹

For **2i**: $^1\text{H NMR}$ (CDCl_3 , 400 MHz) : δ = 7.76-7.74 (m, 2H), 7.53-7.45 (m, 1H), 7.41-7.37 (m, 2H), 5.02 (q, 2H, J = 2.9 Hz), 2.47 (t, 3H, J = 2.9 Hz); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) : δ = 217.7, 195.3, 138.3, 132.1, 129.2, 128.0, 102.2, 78.5, 14.9; **IR** : 3059, 2985, 2927, 1957, 1933, 1646, 1278, 1001, 881, 844, 724, 695, 605 cm^{-1}

(E)-1-Cyclohexyl-3-methoxybut-2-en-1-one (6): To a solution of **1a** (150 mg, 1.00 mmol) in THF (10 mL) was added *n*-BuLi (0.91 mL, 2.00 mmol, 2.20 M in hexanes) at -80°C . After 10 min stirring, the mixture was allowed to warm to -20°C . After 45 min at that temperature, methanol was added and the mixture was stirred 15 min at 0°C . Then 0.5 M HCl and Et_2O was added. The layers were separated and the aqueous one was extracted twice with Et_2O . The combined organic phases were washed with water then brine, and they were dried over MgSO_4 . Evaporation of the solvent and chromatography on silica gel (eluent : 5% Et_2O in pentane) afforded the ketone **6** (138 mg, 0.76 mmol, 76%) as a colourless oil. $^1\text{H NMR}$ (CDCl_3 , 400 MHz) : δ = 5.47 (s, 1H), 3.64 (s, 3H), 2.27 (s, 3H), 2.33-2.20 (m, 1H), 1.83-1.72 (m, 4H), 1.69-1.59 (m, 1H), 1.38-1.12 (m, 5H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) : δ = 202.9, 173.1, 98.0, 55.4, 52.2, 29.1, 26.0, 25.9, 19.7; **IR** : 2926, 2853, 1675, 1581, 1447, 1398, 1262, 1144, 1094, 1066, 792, 755 cm^{-1}

(Z)-(4-Trimethylsilyl-1-trimethylsilyloxybut-1-en-3-ynyl)cyclohexane (7): To a solution of **1a** (75 mg, 0.50 mmol) in THF (5 mL) was added *n*-BuLi (0.50 mL, 1.10 mmol, 2.20 M in hexanes) at -80°C . After 10 min stirring, the mixture was allowed to warm to -20°C . After 45 min at that temperature, chlorotrimethylsilane (0.64 mL, 5.00 mmol) was added and the mixture was stirred 15 min at 0°C . Et_2O (5 mL) was added and the solvents were removed in vacuo. Et_2O was added to the residue, and the solution was filtered. After concentration of the organic layer in vacuo, chromatography on silica gel (pentane) afforded **7** (126 mg, 0.43 mmol, 86%) as a pale yellow oil. $^1\text{H NMR}$ (CDCl_3 , 400 MHz) : δ = 4.73 (s, 1H), 1.91-1.85 (m, 1H), 1.82-1.70 (m, 4H), 1.69-1.62 (m, 1H), 1.29-1.05 (m, 5H), 0.29 (s, 9H), 0.17 (s, 9H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) : δ = 169.5, 103.2, 90.1, 86.7, 45.3, 30.8, 26.3, 26.2, 1.3, 0.3; **IR** : 2929, 2855, 2138, 1621, 1249, 1183, 840, 758 cm^{-1}

1-Cyclohexyl-5-hydroxy-6,6-dimethylhepta-2,3-dien-1-one (8): To a solution of **1a** (75 mg, 0.50 mmol) in THF (5 mL) was added *n*-BuLi (0.50 mL, 1.10 mmol, 2.20 M in hexanes) at -80°C . After 10 min stirring, the mixture was allowed to warm to -20°C . After 45 min, the mixture was cooled down to -40°C and pivaldehyde (0.11 mL, 1.00 mmol) was added. The mixture was stirred 45 min at -20°C . The reaction was then hydrolysed with 0.5 M HCl and diluted with Et_2O . The layers were separated and the aqueous one was extracted twice with Et_2O . The combined organic phases were washed with water then brine, and were dried over MgSO_4 . Evaporation of the solvent and chromatography on silica gel (eluent : 5% Et_2O in pentane) afforded a 50/50 mixture of two diastereoisomers **8** (68 mg, 0.29 mmol, 58%) as a colourless oil. For one diastereoisomer: $^1\text{H NMR}$ (CDCl_3 , 400 MHz) : δ = 5.83 (dd, 1H, J = 6.1 and 2.8 Hz), 5.74 (t, 1H, J = 6.1 Hz), 4.03-3.96 (m, 1H), 2.89-2.78 (m, 1H), 2.03 (d, 1H, J = 4.3 Hz), 1.82-

1.76 (m, 4H), 1.70-1.60 (m, 1H), 1.44-1.14 (m, 5H), 0.99 (s, 9H); ^{13}C NMR (CDCl_3 , 100 MHz) : = 211.4, 204.3, 97.7, 77.6, 47.5, 35.9, 29.5, 29.1, 25.9, 25.8, 25.8, 25.6; IR : 3425, 2930, 2855, 1946, 1660, 1167, 1057, 1013 cm^{-1}

For the other diastereoisomer: ^1H NMR (CDCl_3 , 400 MHz) : = 5.81 (dd, 1H, J = 6.3 and 1.5 Hz), 5.78-5.69 (m, 1H), 4.04-3.92 (m, 1H), 2.85-2.72 (m, 1H), 2.45-2.15 (m, 1H), 1.77-1.74 (m, 4H), 1.69-1.58 (m, 1H), 1.37-1.17 (m, 5H), 0.98 (s, 9H); ^{13}C NMR (CDCl_3 , 100 MHz) : = 212.0, 204.2, 97.2, 96.6, 77.8, 47.4, 35.7, 29.2, 25.9, 25.7, 25.6; IR : 3424, 2930, 2855, 1945, 1660, 1166, 1053, 1007 cm^{-1}

(Z)-1-Cyclohexyl-1,5-trimethylsilyloxy-6,6-dimethylhepta-1-enyne (9): To a solution of **1a** (75 mg, 0.50 mmol) in THF (5 mL) was added *n*-BuLi (0.50 mL, 1.10 mmol, 2.20 M in hexanes) at -80°C . After 10 min stirring, the mixture was allowed to warm to -20°C . After 45 min, the mixture was cooled down to -40°C and pivaldehyde (0.11 mL, 1.00 mmol) was added. The mixture was stirred 45 min at -20°C then chlorotrimethylsilane (0.32 mL, 2.50 mmol) was added and the mixture was stirred 15 min at 0°C . Et_2O (5 mL) was added and the solvents were removed in vacuo. Et_2O was added to the residue, the obtained layer was filtered and the organic layer was concentrated in vacuo to give **9** (162 mg, 87%) as a yellow oil. Chromatography on silica gel (eluent : 2% Et_2O in pentane) afforded **9** (121 mg, 0.32 mmol, 65%) as a pale yellow oil. ^1H NMR (CDCl_3 , 400 MHz) : = 4.70 (d, 1H, J = 2.1 Hz), 4.05 (d, 1H, J = 2.1 Hz), 1.87-1.64 (m, 6H), 1.28-1.09 (m, 5H), 0.94 (s, 9H), 0.26 (s, 9H), 0.14 (s, 9H); ^{13}C NMR (CDCl_3 , 100 MHz) : = 167.1, 91.5, 86.7, 82.2, 72.5, 45.1, 36.6, 31.0, 30.9, 26.4, 26.3, 25.8, 25.3, 1.1, 0.3; IR : 2955, 2929, 2855, 2209, 1628, 1250, 1069, 965, 882, 839, 751 cm^{-1}

211.4336

204.3048

97.7239
97.1241

77.5542
77.4770
77.1600
76.8430

47.4881

35.9209

29.4604
29.0920
25.9303
25.8274
25.7503
25.6389