New Tandem Zn-Promoted Brook Rearrangement / Ene-Allene carbocyclization Reactions.

Rozalia Unger‡, Theodore Cohen† and Ilan Marek‡*  

‡ The Mallat Family Laboratory of Organic Chemistry  
Department of Chemistry, Institute of Catalysis Science and Technology  
The Lise Meitner-Minerva Center for Computational Quantum Chemistry  
Technion-Israel Institute of Technology  
Technion City, Haifa 32 000 Israel  
Email: chilanm@tx.technion.ac.il

† Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Experimental Part

General

All reactions involving air- and moisture-sensitive compounds were carried out under argon atmosphere, usingflamed flask and dry, oxygen-free solvents. Diethyl ether and tetrahydrofuran were distilled under argon from sodium benzophenone ketyl. CH₂Cl₂ was distilled from CaH₂. n-BuLi was commercially obtained from Aldrich and titrated under argon atmosphere by 1M solution of 2-isobutanol in toluene, using 2,2'-biquinoline as indicator. All Grignard reagents were prepared and titrated under argon atmosphere by 1M solution of 2-isobutanol in toluene, using 2,2'-biquinoline as indicator. All NMR spectra were recorded at room temperature with a Bruker-AC-200, Bruker-Avance-300 and 500 MHz instruments. Chemical shifts are referenced to the residual proton or carbon resonance of the deuteriated solvent and are reported relative to Si(CH₃)₄.

Preparation of acylsilanes 4, 15 and 21 were prepared from literature. All the NMR data of our compounds were correlated with data from literature (see references cited therein).

Silane, trimethyl(1-oxo-5-hexenyl) 15 ¹H NMR (CDCl₃, 300 MHz) δ 0.12 (s, 9 H), 1.55 (q, J = 7.2 Hz, 2 H), 1.95 (t, J = 7.2 Hz, 2 H), 2.53 (t, J = 7.2 Hz, 2 H), 4.86-4.96 (m, 2 H), 5.57-5.78 (m, 1 H); ¹³C NMR (CDCl₃, 100 MHz) δ -3.3, 21.1, 33.1, 47.4, 114.9, 138.1, 247.0

Silane, trimethyl(1-oxo-6-trimethylsilyl-5-hexenyl) 21 ¹H NMR (CDCl₃, 300 MHz) δ 0.13 (s, 9 H), 0.17 (s, 9 H), 1.67 (q, J = 7.1 Hz, 2 H), 2.20 (dt, J₁ = 7.0 Hz, J₂ = 0.9 Hz, J₃ = 7.0 Hz, 2 H), 4.86-4.96 (m, 2 H), 5.57-5.78 (m, 1 H); ¹³C NMR (CDCl₃, 100 MHz) δ -3.3, 21.1, 33.1, 47.4, 114.9, 138.1, 247.0


2H), 2.72 (dt, \( J_1 = 7.2 \) Hz, \( J_2 = 0.9 \) Hz, 2H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) -2.9, -3.2, 17.8, 20.7, 29.7, 46.6, 68.9, 83.8, 247.6.

**General procedure for the zinc induced Brook rearrangement**

To a cold (0°C) stirred solution of terminal alkyne in THF was added drop wise EtMgBr solution in Et\(_2\)O (1 equiv., 1N solution in Et\(_2\)O). The mixture was first warmed to room temperature for 90 min and then cooled down to –80°C to introduce very slowly acylsilane 4 over a period of 30 min. After the addition was completed, the mixture was refluxed for 45 min, and a ZnBr\(_2\) solution in THF (1 equiv., 1N solution in THF) was added at –60°C. The reaction mixture was either warm to room temperature for 5c or heated at 40°C for 5a and 5b for few hours (the evolution is followed by gas chromatography analyses of hydrolyzed aliquots). The reaction was hydrolyzed with an aqueous solution of HCl (1M). The organic phase was washed with NaHCO\(_3\), and stirred for at least 3 hours with a few Na\(_2\)S\(_9\)H\(_2\)O crystals that enabled the removal of all zinc salts before further purification. These were then removed by filtration, and the organic solution was washed with brine (2x15ml), dried over MgSO\(_4\) and concentrated under vacuum. Purification was performed by column chromatography on silica gel using EtOAc/hexane as eluent.

4-undecene-3-one, 1-phenyl-(4E)\(^d\) 7c The reaction was performed as described above in the typical experimental procedure for the Zn-promoted Brook rearrangement: Octyne (1.2 mmol, 0.18 mL), BuMgBr (1 equiv. 1N sol/Et\(_2\)O, 1.2 mmol, 1.2 mL), silane, trimethyl(1-oxo-3-phenylpropyl) (1 mmol, 0.220 gr), ZnBr\(_2\) (1.2 eq., 1 N solution in THF, 1.2 ml). After purification by column chromatography, 0.167 gr (68%) of product 7c was obtained as a colorless liquid. \(^1\)H NMR (CDCl\(_3\), 300 MHz) \( \delta \) 0.91-0.95 (m, 3H), 1.33-1.35 (m, 6H), 1.47-1.49 (m, 2H), 1.99 (quin, \( J = 7.5 \) Hz, 2H), 2.23 (q, \( J = 6.6 \) Hz, 2H), 2.59 (t, \( J = 7.35 \) Hz, 2H), 2.69 (t, \( J = 7.8 \) Hz, 2H), 2.612 (dt, \( J = 15.9 \) Hz, \( J = 1.5 \) Hz, 1H), 6.83 (dt, \( J = 2.1 \) Hz, \( J = 7.95 \) Hz, 1H), 7.23–7.35 (m, 5H). \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \( \delta \) 14.0, 22.5, 25.7, 28.0, 29.3, 31.9, 32.4, 35.2, 39.2, 125.9, 128.3, 128.5, 130.2, 141.7, 147.5, 200.5. HRMS (C\(_{18}\)H\(_{26}\)O, EI M\(^+\) m/z); Calculated, 258.1984; Found, 258.1984.

1-Penten-3-one, 1,5-diphenyl (1E)\(^5\) 7b The reaction was performed as described above in the typical experimental procedure for the Zn-promoted Brook rearrangement: Phenylacetylene (1.2 mmol, 0.13 mL), BuMgBr (1 equiv. 1N sol/Et\(_2\)O, 1.2 mmol, 1.2 mL), silane, trimethyl(1-oxo-3-phenylpropyl) (1 mmol, 0.220 gr), ZnBr\(_2\) (1.2 eq., 1 N solution in THF, 1.2 ml). After purification by column chromatography, 0.196 gr (85%) of products 7b and 8b were obtained as a colorless liquid. \(^1\)H NMR (C\(_6\)D\(_6\), 300 MHz) \( \delta \) 1.39-1.46 (dt, \( J_1 = 11.6 \) Hz, \( J_2 = 1.7 \) Hz 2H), 1.90 (t, \( J = 9.8 \) Hz), 6.49 (d, \( J = 21 \) Hz, 1H), 7.17-7.33 (m, 10H), 7.61 (d, \( J = 21.1 \) Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \( \delta \) 30.0, 42.3, 126.0, 126.0, 128.1, 128.3, 128.4, 128.8, 130.4, 134.3, 141.1, 142.5, 199.1; IR (CHCl\(_3\))

---


1-Penten-3-one, 5-phenyl-1E-(trimethylsilyl)$^6$ 7a The reaction was performed as described above in the typical experimental procedure for the Zn-promoted Brook rearrangement: Trimethylsilyl acetylene (1.2 mmol, 0.17 mL), BuMgBr (1 equiv. 1N sol/Et$_2$O, 1.2 mmol, 1.2 mL), silane, trimethyl(1-oxo-3-phenylpropyl) (1 mmol, 0.220 gr), ZnBr$_2$ (1.2 eq., 1 N solution in THF, 1.2 ml). After purification by column chromatography, 0.213 gr (90%) of products 7a and 8a were obtained as a colorless liquid. $^1$H NMR (C$_6$D$_6$, 300 MHz) $\delta$ 0.04 (s, 9H), 2.605 (t, $J = 7.7$ Hz, 2H), 2.98 (t, $J = 7.7$ Hz, 2H), 6.50 (d, $J = 19.5$ Hz, 1H), 6.96 (d, $J = 19.2$ Hz, 1H), 7.10–7.18 (m, 5H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ -1.9, 30.0, 41.0, 126.1, 128.4, 128.5, 141.2, 142.1, 147.0, 199.4; IR (CHCl$_3$) 3030, 3010, 1688, 1659, 1609, 1577, 1495, 1451, 1366, 1329, 1302, 1176, 1097, 1072, 976, 699.

Benzenepropanol, $\alpha$-[(trimethylsilyl)ethynyl] 7$^8$ 8a: $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 0.12 (s, 9H), 1.68 (s, 1H), 1.92–2.00 (m, 2H), 2.73 (t, $J = 7.8$ Hz, 2H), 4.30 (t, $J = 6.6$ Hz, 1H), 7.13–7.25 (m, 5H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ -0.1, 31.4, 39.2, 62.2, 89.9, 106.4, 126.0, 128.4, 128.5, 141.3.

General procedure for the Brook rearrangement followed by zinc-ene-allene cyclization.

To a cold (0°C) stirred solution of terminal alkyne in THF was added drop wise EtMgBr solution in Et$_2$O (1 equiv., 1N solution in Et$_2$O). The mixture was first warmed to room temperature for 90 min and then cooled down to $-80^\circ$C to introduce very slowly the acylsilane 15 (or 21) over a period of 30 min. After the addition was completed, the mixture was refluxed for 45 min, and a ZnBr$_2$ solution in THF (1 equiv., 1N solution in THF) was added at $-60^\circ$C. The reaction mixture was either warm to room temperature for 5c or heated at 40°C for 5a and 5b for few hours (the evolution is followed by gas chromatography analyses of hydrolyzed aliquots). The reaction mixture was cooled to $-5^\circ$C as 1 M hydrochloric acid (10 mL) was added slowly. Ether was added and the layers were separated, the aqueous one being extracted with ether. The combined extracts were washed with saturated NaHCO$_3$, and stirred for at least 3 hours with a few Na$_2$S.9H$_2$O crystals that enabled the removal of all zinc salts before further purification. These were then removed by filtration, and the organic solution was washed with brine (2x15 mL), dried over MgSO$_4$ and concentrated.

Silane, trimethyl[[f[cis-1-(trimethylsilyl)ethynyl]-2-methyl-cyclopentyl]oxy] 19$^8$ The tandem reaction was performed as described above in the typical experimental procedure: Trimethylsilyl acetylene (1.2 mmol, 0.17 mL), BuMgBr (1 equiv. 1N sol/Et$_2$O, 1.2 mmol, 1.2 mL), silane, trimethyl(1-oxo-5-hexenyl) (1 mmol, 0.170 gr), ZnBr$_2$ (1.2 eq., 1 N solution in THF, 1.2 ml). After purification by column chromatography, 0.239 gr (89%) of product 19a was obtained as a colorless liquid. $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 0.13 (s, 9H), 0.15 (s, 9H), 0.96 (d, $J = 6.6$ Hz, 3H), 1.23-1.28 (m, 1H), 1.60-1.68 (m, 2H), 1.73-

The tandem reaction was performed as described above in the typical experimental procedure: phenyl acetylene (1.2 mmol, 0.16 mL), BuMgBr (1.2 mL, 1N sol/Et₂O, 1.2 mmol), silane, trimethyl(1-oxo-5-hexenyl) (1 mmol, 0.170 gr), ZnBr₂ (1.2 eq., 1 N solution in THF, 1.2 mL). After purification by column chromatography, 0.141 gr (70%) of product 19b was obtained as a colorless liquid. ¹H NMR (CDCl₃, 300 MHz) δ 1.10 (d, J = 6.6 Hz, 3H), 1.36-1.45 (m, 1H), 1.56 (s, 1H), 1.70-1.78 (m, 2H), 1.91-2.21 (m, 4H), 7.27–7.42 (m, 5H); ¹³C NMR (CDCl₃, 100 MHz) δ 16.5, 20.6, 31.2, 40.9, 46.1, 78.9, 85.9, 90.6, 122.9, 128.2, 128.2, 131.6; HRMS (C₁₄H₁₆O, EI M⁺ m/z); Calculated 200.1201; Found.

Cyclopentanol, 2-methyl-1-(phenylethynyl)-, trans 19b⁹ The tandem reaction was performed as described above in the typical experimental procedure: cyclopentanol, 2(E)-[(trimethylsilyl)methylidene]-1-[(trimethylsilyl)-1-ethynyl]⁵⁻¹² 25a The tandem reaction was performed as described above in the typical experimental procedure: phenyl acetylene (1.2 mmol, 0.16 mL), BuMgBr (1.2 mL, 1N sol/Et₂O, 1.2 mmol), silane, trimethyl(1-oxo-5-hexenyl) (1 mmol, 0.170 gr), ZnBr₂ (1.2 eq., 1 N solution in THF, 1.2 mL). After purification by column chromatography, 0.141 gr (70%) of product 19b was obtained as a colorless liquid. ¹H NMR (CDCl₃, 300 MHz) δ 1.10 (d, J = 6.6 Hz, 3H), 1.36-1.45 (m, 1H), 1.56 (s, 1H), 1.70-1.78 (m, 2H), 1.91-2.21 (m, 4H), 7.27–7.42 (m, 5H); ¹³C NMR (CDCl₃, 100 MHz) δ 16.5, 20.6, 31.2, 40.9, 46.1, 78.9, 85.9, 90.6, 122.9, 128.2, 128.2, 131.6; HRMS (C₁₄H₁₆O, EI M⁺ m/z); Calculated 200.1201; Found.

Cyclopentanol, 2-methyl-1-(1-octynyl), trans 19c⁹ The tandem reaction was performed as described above in the typical experimental procedure: octyne (1.2 mmol, 0.18 mL), BuMgBr (1.2 mL, 1N sol/Et₂O, 1.2 mmol), silane, trimethyl(1-oxo-5-hexenyl) (1 mmol, 0.170 gr), ZnBr₂ (1.2 eq., 1 N solution in THF, 1.2 mL). After purification by column chromatography, 0.107 gr (50%) of product 19c was obtained as a colorless liquid. ¹H NMR (CDCl₃, 300 MHz) δ 0.83-0.88 (d, J = 6.8 Hz, 3H), 1.0 (d, J = 6.6 Hz, 3H), 1.23-1.45 (m, 7H + 1H, OH), 1.45-1.48 (m, 2H), 1.66-1.69 (m, 2H), 1.85-2.05 (m, 4H), 2.21 (t, J = 6.9 Hz, 2H); ¹³C NMR (CDCl₃, 75 MHz) δ 14.0, 16.4, 18.7, 20.4, 22.5, 28.5, 28.8, 31.0, 31.3, 41.0, 45.7, 78.6, 81.5, 114.5.

Silane, trimethyl[(cis-1-(trimethylsilylthethyl)-2-iodomethyl-cyclopentyl]oxy] 20a¹¹ The tandem reaction was performed as described above in the typical experimental procedure but instead of hydrolysis, I₂ (2 equiv) was added at -30°C in 10 mL of THF. The reaction was warmed to room temperature, stirred for an additional 2 hours and the hydrolysis and further treatment are done as usual. Trimethylsilyl acetylene (1.2 mmol, 0.17 mL), BuMgBr (1 equiv. 1N sol/Et₂O, 1.2 mmol, 1.2 mL), silane, trimethyl(1-oxo-5-hexenyl) (1 mmol, 0.170 gr), ZnBr₂ (1.2 eq., 1 N solution in THF, 1.2 mL), iodine (2 equiv., 2.4 mmol, 0.65 gr). After purification by column chromatography, 0.199 gr (60%) of product 20a was obtained as a colorless liquid. ¹H NMR (CDCl₃, 300 MHz) δ 0.04 (s, 9H), 0.15 (s, 9H), 1.90-2.0 (m, 2H), 2.07-2.20 (m, 3H), 2.29-2.34 (m, 2H), 3.08 (t, J = 9.3 Hz, 1H), 3.45 (dd, J₁ = 9.6 Hz, J₂ = 3.6 Hz, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ -0.1, 1.0, 7.2, 20.0, 31.4, 42.4, 53.2, 77.7, 91.8, 105.5. HRMS (C₁₁H₁₉IOSi, EI M⁺ m/z); Calculated, 322.0250; Found.
procedure: Trimethylsilyl acetylene (1.2 mmol, 0.17 mL), BuMgBr (1 equiv. 1N sol/Et₂O, 1.2 mmol, 1.2 mL), silane, trimethyl(1-oxo-6-trimethylsilyl-5-hexenyl) (1 mmol, 0.240 gr), ZnBr₂ (1.2 eq., 1 N solution in THF, 1.2 ml). After purification by column chromatography, 0.200 gr (75%) of product 25a was obtained as a colorless liquid. 'H NMR (CDCl₃, 300 MHz) δ 0.10 (s, 9H), 0.17 (s, 9H), 1.74-2.04 (m, 4H), 2.34-2.43 (m, 1H), 2.48-2.53 (m, 1H), 5.930 (t, J = 2.6 Hz, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ -0.7, -0.1, 22.0, 29.7, 41.2, 62.5, 89.2, 107.9, 121.6, 163.1; HRMS (C₁₄H₂₆OSi₂, El M⁺ m/z); Calculated 266.1522 ; Found.

Cyclopentanol, 2(E)-[(trimethylsilyl)-methylidene]-1-(phenylethynyl)

25b The tandem reaction was performed as described above in the typical experimental procedure: phenyl acetylene (1.2 mmol, 0.13 mL), BuMgBr (1 equiv. 1N sol/Et₂O, 1.2 mmol, 1.2 mL), silane, trimethyl(1-oxo-6-trimethylsilyl-5-hexenyl) (1 mmol, 0.240 gr), ZnBr₂ (1.2 eq., 1 N solution in THF, 1.2 ml). After purification by column chromatography, 0.176 gr (65%) of product 25b was obtained as a colorless liquid. 'H NMR (CDCl₃, 300 MHz) δ 1.56 (s, 1H), 1.70-1.78 (m, 2H), 1.91-2.21 (m, 4H), 5.96 (t, J = 2.6 Hz, 1H), 7.27–7.42 (m, 5H); ¹³C NMR (CDCl₃, 75 MHz) δ -0.7, 20.6, 29.7, 40.9, 78.9, 85.9, 90.6, 122.3, 122.9, 128.2, 128.2, 163.0.

---