Supporting Information

Diastereoselectivity in the Reduction of α -Oxy and α -Amino Substituted Acyclic Ketones by Polymethylhydrosiloxane

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Experimental Section

All ^1H and ^{13}C NMR spectra were recorded in CDCl_3 solvent at 400 MHz and 100 MHz respectively with chloroform (^1H , 7.26 ppm; ^{13}C , 77.0 ppm) as an internal standard.

High-resolution mass spectra of amino alcohols were obtained using time-of-flight mass spectrometer with electrospray ionization in the positive mode using laudanosine and CP-331684 as internal standards for amino alcohols and oxy-substituted alcohols respectively. Column chromatography was performed using silica gel 60. Analytical TLC was performed on silica gel (250 micron) TLC plates. Polymethylhydrosiloxane [PMHS, $-(\text{CH}_3\text{SiHO})_n-$ where $n \sim 35$] and tetrabutylammonium fluoride (1M solution in THF) were purchased from commercial sources. Commercially available BHT stabilized tetrahydrofuran (THF) was used as solvent without further purification. The diastereomeric ratios of amino alcohol products were determined by direct comparison to literature examples and by integration of diagnostic peaks resulting from $-\text{CHOH}-$ protons in ^1H NMR spectra of the isolated crude product mixture. For vicinal amino alcohols the methine proton ($-\text{CHOH}-$) of the anti diastereomer is downfield compared to methine proton of the syn diastereomer.¹ Also syn and anti diastereomers are

distinguishable by the coupling constants of vicinal protons ($-\text{CH}\underline{\text{O}}\text{H}-$ and $-\text{CH}\underline{\text{N}}\text{H}-$). For syn (threo) and anti (erythro) amino alcohols the coupling constants are in the range of 8-11 Hz and 3-5 Hz respectively. These values are comparable to the coupling constant values observed for pseudoephedrine and ephedrine.^{1,2} The relative configurations of products obtained from reduction of α -oxy substituted ketones were determined by comparison of their proton and ^{13}C NMR spectra to literature reported values.

General procedure for reduction of ketones with PMHS catalyzed by TBAF:

To a clean dry flask equipped with a thermometer, a magnetic stirrer, and an addition funnel were added ketone (5 mmol, 1 equiv), THF (25 mL) and PMHS (0.2-0.3 mmol, 2-2.5 hydride equivalents). The solution was cooled to 0 to $-5\text{ }^{\circ}\text{C}$ in ice-acetone bath. Tetrabutylammonium fluoride (5 mol % with respect to ketone) solution was added to the reaction mixture slowly with syringe over 15 minute period maintaining the temperature between 0- $5\text{ }^{\circ}\text{C}$. The reaction mixture was stirred at 0- $5\text{ }^{\circ}\text{C}$ for 2 hours. After TLC indicated disappearance of starting ketone additional solution of TBAF (5 mmol, 1equiv.) was slowly added to the reaction mixture. The reaction mixture was allowed to warm up to room temperature over 1 hour. Solvent was evaporated to dryness on rotary evaporator. The residue was dissolved in 25 mL of methylene chloride. The methylene chloride solution was stirred with 25 mL of water for 1 hour. Layers were separated and organic layer was washed with water (15 mL). Methylene chloride solution was dried over sodium sulfate, filtered and evaporated to dryness to furnish crude product. All crude products were purified by column chromatography on silica gel using ethylacetate/hexane solvent mixture.

Reduction of 1-phenyl-2-piperidin-1-yl-1-propanone (1a): Ketone **1a** (1.0 g, 4.6 mmol) was reduced with PMHS (0.5 g, 1.5 equiv.) in THF (25 mL) in the presence of TBAF (0.23 ml of 1 M solution in THF, 5 mol %) according to the above general procedure. The crude product was purified by column chromatography on silica gel with hexane/ethylacetate (4:1) as eluent. (0.807 g, 80 % yield as a syn-diastereomer, **2a**).³

2a: ¹H NMR: δ 0.73 (d, 3H, J = 6.0 Hz), 1.46–1.67 (m, 6H), 2.37 (m, 2H), 2.50 (m, 1H), 2.66 (m, 2H), 4.21 (d, 1H, J = 9.5 Hz), 7.22–7.35 (m, 5H).

¹³C NMR: 8.21, 24.77, 26.60 (2C), 49.82 (2C), 67.21, 74.45, 127.59 (2C), 127.89, 128.44 (2C), 142.42.

HRMS: m/z Calcd for C₁₄H₂₁NO (M⁺ + H) 220.1701. Found: 220.1700.

Reduction of 2-diethylamino-1-phenyl-1-propanone (1b): Ketone **1b** (1 g, 4.9 mmol) was reduced with PMHS (0.8 g, 2.5 equiv.) in THF (25 mL) in the presence of TBAF (0.25 mL, 5 mol %) according to the general procedure above. The crude product was purified by column chromatography on silica gel with hexane/ethylacetate (4:1) as eluent. (0.760 g, 76 % yield as the syn-diastereomer **2b**).⁴

2b: ¹H NMR: δ 0.75 (d, 3 H, J = 6.7 Hz), 1.12 (t, 6 H, J = 7.3 Hz), 2.39 (m, 2 H), 2.70 (m, 3 H), 4.18 (d, 1 H, J = 9.5 Hz), 5.10 (br, 1 H, OH), 7.23–7.37 (m, 5 H).

¹³C NMR: 8.64, 14.58 (2C), 43.22 (2C), 62.39, 74.63, 127.55 (2C), 127.80, 128.40 (2C), 142.78.

HRMS: m/z Calcd for C₁₃H₂₁NO (M⁺ + H) 208.1701. Found: 208.1707.

Reduction of 2-(benzylmethylamino)-1-phenyl-1-propanone (1c):

Ketone **1c** (1 g, 3.95 mmol) was reduced with PMHS (0.645 g, 2.5 equiv.) in THF (25 mL) in the presence of TBAF (0.20 mL, 5 mol %) according to the above general

procedure. The crude product was purified by column chromatography on silica gel with hexane/ethylacetate (4:1) as eluent (0.877 g, 87 % yield as the syn-diastereomer **2c**).⁵

2c: ¹H NMR: δ 0.86 (d, 3H, J = 6.6 Hz), 2.23 (s, 3H), 2.82 (m, 1H), 3.54 (d, 1H, J = 13.3 Hz), 3.80 (d, 1H, J = 13.3 Hz), 4.39 (d, 1H, J = 10.0 Hz), 5.29 (br, 1H), 7.30 – 7.43 (m, 10H).

¹³C NMR: δ 7.64, 36.02, 58.53, 65.17, 75.08, 127.64, 127.70 (2C), 128.02, 128.16, 128.54 (2C), 128.80, 128.94, 129.27, 138.95, 142.33.

HRMS: m/z Calcd for C₁₇H₂₁NO (M⁺ + H) 256.1701. Found: 220.1696.

Reduction of 2-dibenzylamino-1-phenyl-1-propanone (1d):

Ketone **1d** (1.1 g, 4.5 mmol) was reduced with PMHS (0.556 g, 2.5 equiv.) in THF (25 mL) in the presence of TBAF (0.22 mL, 5 mol %) according to the general procedure above. The crude product was purified by column chromatography on silica gel with hexane/ethylacetate (95:5) as eluent. (1.05 g, 95 % yield as syn-diastereomer **2d**).^{5a}

2d: ¹H NMR: δ 0.98 (d, 3H, J = 6.7 Hz), 2.93 (1H, m), 3.47 (d, 2H, J = 13.3 Hz), 4.06 (d, 2H, J = 13.3 Hz), 4.54 (d, 1H, J = 9.6 Hz), 5.21 (1H, br, OH), 7.28-7.48 (m, 15H).

¹³C NMR: δ 8.18, 53.73, 60.61 (2C), 74.81, 127.72 (2C), 127.77 (2C), 128.04, 128.57 (2C), 128.99 (4C), 129.54 (4C), 139.17 (2C).

HRMS: m/z Calcd for C₂₃H₂₅NO (M⁺ + H) 332.2014. Found: 332.2002.

Reduction of 2-benzylamino-1-phenyl-1-propanone (1e):

Ketone **1e** (1.0 g, 4.18 mmol) was reduced with PMHS (0.7 g, 2.5 equiv.) in THF (25 mL) in the presence of TBAF (0.21 mL, 5 mol %) according to the general procedure above. The crude product was purified by column chromatography on silica gel with

hexane/ethylacetate (1:3) as eluent. (0.890 g, 88 % yield as mixture of diastereomers,

2e:3e 26:74).^{5a, 6}

2e: ¹H NMR: δ 1.00 (d, 3H, J = 6.3 Hz), 2.83 (m, 1H), 3.23 (br. 2H), 4.26 (d, 1H, J = 8.3 Hz), 3.73 (d, 1H, J = 13.3 Hz), 3.92 (d, 1H, J = 13.3 Hz), 7.24-7.38 (m, 10H).

3e: ¹H NMR: δ 0.90 (d, 3H, J = 6.6 Hz), 3.00 (m, 1H), 3.23 (br, 2H), 3.88 (d, 2H, J = 2.1 Hz), 4.82 (d, 1H, J = 4.2 Hz), 7.24-7.38 (m, 10H).

HRMS: m/z Calcd for C₁₆H₁₉NO (M⁺ + H) 242.1545. Found: 242.1537.

Reduction of 2-acetoxypropiophenone (**1f**):

Ketone **1f** (1.0 g, 5.21 mmol) was reduced with PMHS (0.85 g, 2.5 equiv.) in THF (25 mL) in the presence of TBAF (0.26 mL, 5 mol %) according to the general procedure above. After cleavage of the intermediate silyl ether with TBAF (5.21 mL) the solvent was evaporated on rotary evaporator. The residue was dissolved in 20 mL of methanol and 5 mL of 20 % (w/w) aqueous sodium hydroxide solution. The solution was stirred at 25 °C for 2 hours. Solvent was evaporated on rotary evaporator. The residue was dissolved in methylene chloride (25 mL). The methylene chloride solution was washed with water (25 mL X 2), dried over sodium sulfate and evaporated to dryness affording crude product as diol. The product was purified by column chromatography over silica gel with hexane/ethylacetate (50:50) as eluent (0.768 g, 76 % yield as mixture of diastereomers **2f:3f** 97:3).⁷

2f: ¹H NMR: δ 0.93 (d, 3H, J = 6.2 Hz), 3.75 (m, 1H), 3.98 (br, s, 2H), 4.23 (d, 1H, J = 7.9 Hz), 7.24-7.31 (m, 5H).

HRMS: m/z Calcd for C₉H₁₂O₂ (M⁺ + Na) 175.0735. Found: 175.0743.

Reduction of 2-benzoyloxypropioiphenone (1g):

Ketone **1g** (1.0 g, 3.94 mmol) was reduced with PMHS (0.384 g, 1.5 equiv.) in THF (25 mL) in the presence of TBAF (0.20 mL, 5 mol %) according to the general procedure above. After cleavage of intermediate silyl ether with TBAF (5.0 mL) the solvent was evaporated on rotary evaporator. The residue was dissolved in 20 mL of methanol and 5 mL of 20 % (w/w) aqueous sodium hydroxide solution. The solution was stirred at 25 °C for 2 hours. Solvent was evaporated on rotary evaporator. The residue was dissolved in methylene chloride (25 mL). The methylene chloride solution was washed with water (25 mL X 2), dried over sodium sulfate and evaporated to dryness affording crude product as diol. The product was purified by column chromatography over silica gel with hexane/ethylacetate (50:50) as eluent (0.715 g, 71 % yield as mixture of diastereomers **2f:3f** 97:3).

Reduction of 2-methoxy-1-phenyl-1-propanone (1h):

Ketone **1h** (0.5 g, 3.05 mmol) was reduced with PMHS (0.396 g, 2.0 equiv.) in THF (25 mL) in the presence of TBAF (0.15 mL, 5 mol %) according to the general procedure above. The crude product was purified by column chromatography over silica gel with hexane/ethylacetate (90:10) as eluent (0.389 g, 77% yield as mixture of diastereomers **2h:3h** 87:13).⁸

2h: ¹H NMR: δ 0.94 (d, 3H, J = 6.2 Hz), 3.34 (br, s, 1H), 3.36 (m, 1H), 3.39 (s, 3H), 4.37 (d, 1H, J = 7.9 Hz), 7.24-7.34 (m, 5H)

3h: ¹H NMR: δ 0.97 (d, 3H, J = 6.6 Hz), 3.34 (br, s, 1H), 3.36 (s, 3H), 3.50 (m, 1H), 4.85 (d, 1H, J = 3.7 Hz) 7.24-7.34 (m, 5H).

HRMS: m/z Calcd for C₁₀H₁₄O₂ (M⁺ + Na) 189.0891. Found: 189.0889.

Reduction of (S)- 3-benzyloxy-2-butanone (**1i**):

Ketone **1i** (1.0 g, 5.6 mmol) was reduced with PMHS (1.1 g, 3 equiv.) in THF (25 mL) in the presence of TBAF (0.28 mL, 5 mol %) according to the above general procedure.

The crude product was purified by column chromatography over silica gel with hexane/ethylacetate (75:25) as eluent [0.850 g, 79% yield as mixture of diastereomers syn **2i** (2S,3S) : anti **3i** (2R, 3S) 73:27]⁹. The enantiomeric purity of the product mixture was determined by comparison to the racemic mixture¹⁰ of **2i** and **3i** by chiral HPLC with Chiracel OD as chiral column (detector:254 nm, hexane:isopropanol 99.6:0.4 v/v, 1.5 mL/min flow rate, column temperature 35 °C). Retention times: syn (2S, 3S) = 14.6 minutes, syn (2R, 3R) = 15.3 minutes, anti (2R, 3S) = 19.4 minutes, anti (2S, 3R) = 27.4 minutes.

2i: ¹H NMR: δ 1.15 (d, 3H, J = 6.2 Hz), 1.16 (d, 3H, J = 5.8 Hz), 3.31 (m, 1H), 3.62 (m, 1H), 4.44 (d, 1H, J = 11.6 Hz), 4.65 (d, 1H, J = 11.6 Hz), 7.24-7.35 (m, 5H).

3i: ¹H NMR: δ 1.13 (m, 6H), 3.50 (m, 1H), 3.90 (m, 1H), 4.49 (d, 1H, J = 12.0 Hz), 4.60 (d, 1H, J = 12.0 Hz), 7.24-7.35 (m, 5H).

HRMS: m/z Calcd for C₁₁H₁₆O₂ (M⁺ + Na) 203.1048. Found: 203.1047.

Reduction of 3-dibenzylamino-2-butanone (**1j**):

Ketone **1j** (0.943 g, 3.74 mmol) was reduced with PMHS (0.73 g, 3.0 equiv.) in THF (25 mL) in the presence of TBAF (0.19 mL, 5 mol %) according to the general procedure above. The crude product was purified by column chromatography on silica gel with hexane/ethylacetate (95:5) as eluent. (0.860 g, 90 % yield as syn diastereomer **2j**). The ratio of diastereomers was determined by proton NMR spectrum of the crude product syn **2j**:anti **3j**, 95:5).¹¹

2j: ^1H NMR: δ 1.02 (d, 3H, $J = 6.6$ Hz), 1.11 (d, 3H, $J = 5.8$ Hz), 2.52 (m, 1H, $J = 6.6$ Hz, $J = 9.1$ Hz), 3.32 (d, 2H, $J = 13.3$ Hz), 3.65 (m, 1H, $J = 5.8$ Hz, $J = 9.1$ Hz), 3.85 (d, 2H, $J = 13.3$ Hz), 4.39 (s, 1H), 7.25–7.36 (m, 5H).

^{13}C NMR: δ 8.18, 19.71, 53.63, 60.55 (2C), 67.25, 127.52 (2C), 128.78 (4C), 129.31 (4C), 139.30 (2C).

HRMS: m/z Calcd for $\text{C}_{18}\text{H}_{23}\text{NO}$ ($\text{M}^+ + \text{H}$) 270.1858. Found: 270.1862.

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