Directed Reductive Amination of β -Hydroxy-Ketones: Convergent Assembly of the Ritonavir/Lopinavir Core

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General experimental procedures

1. Synthesis of β -hydroxy-ketones

A solution of LDA (1.5 M in hexane, 1.05 eq., 10.5 mmol, 7 mL) in Et₂O (5 mL) was treated at -78 °C with a solution of the ketone (10.0 mmol) in Et₂O (10 mL). After 60 min, a solution of the aldehyde (10.0 mmol) in Et₂O (10 mL) was added. After 10 min at the same temperature, the reaction mixture was cannulated into pH-7 buffer (20 mL). The organic phase was separated, and the aq. phase thoroughly extracted with Et₂O. Drying of the combined organic extracts (MgSO₄), evaporation of the solvent and flash chromatography using mixtures of petroleum ether/ethyl acetate gave the respective β -Hydroxy-Ketones with the indicated yields.

2. Directed reductive amination

Typical Procedure: A mixture of β -hydroxy ketone (1.00 mmol), *p*-anisidine (**8**, 2.00 mmol, 246 mg) and titanium(IV) isopropoxide (1.40 mmol, 398 mg, 440 μ L) in acetonitrile (5 mL) was stirred under argon at -20 °C for 1 h. At this temperature, a solution of polymethylhydrosiloxane (134 mg, 2.2 mmol) in acetonitrile (1 mL) was added and the resulting mixture was stirred until complete conversion. The reaction mixture was treated with 5 mL aq. NaOH solution (1M) and under stirring warmed to room temperature. The solution was thoroughly extracted with ether. The combined organic phases were washed with brine, dried (MgSO₄) and the solvent evaporated *in vacuo*. The diastereomeric ratio was determined by HPLC or NMR (see Supporting Information). Purification of the crude products by flash chromatography using mixtures of ethyl acetate / petroleum ether gave analytical samples of the 1,3-*syn* amino alcohols with the yields given (see Figure 2 of the manuscript).

Spectroscopic data and copies of spectra for all new compounds**5-Hydroxy-2,6-dimethyl-heptan-3-one (7)**

Yield: 72%; ^1H NMR (400 MHz, CDCl_3) δ 0.90 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 7.1 Hz, 3H), 1.10 (d, J = 7.1 Hz, 6H), 1.67 (sept d, J = 6.8, 5.6 Hz, 1H), 2.50 (dd, J = 17.2 Hz, J = 9.6 Hz, 1H), 2.60 (sept, J = 7.1 Hz, 1H), 2.62 (dd, J = 17.2 Hz, J = 2.5 Hz, 1H), 3.01 (br s, 1H), 3.78 (ddd, J = 9.6 Hz, J = 5.6 Hz, J = 2.5 Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 17.8, 18.1, 18.4, 33.0, 41.6, 43.6, 72.3, 216.6 MS (ESI) m/z 159 (100) $[\text{M}+\text{H}^+]$. The spectroscopic data were in agreement with those previously reported.¹

(*syn*)-5-(4-Methoxy-phenylamino)-2,6-dimethyl-heptan-3-ol (9)

^1H NMR (400 MHz, CDCl_3) δ 0.82 (d, J = 6.8 Hz, 3H), 0.89 (d, J = 7.0 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 1.25 (ddd, J = 14.3, 10.2, 10.2 Hz, 1H), 1.58-1.74 (m, 2H), 1.92 (dd, J = 7.0, 2.6 Hz, 1H), 3.34 (ddd, J = 10.2, 2.6, 2.6 Hz, 1H), 3.62 (ddd, J = 10.2, 5.1 Hz, J = 2.1 Hz, 1H), 3.73 (s, 3H), 6.68 (ddd, J = 9.4, 3.1, 2.8 Hz, 2H), 6.76 (ddd, J = 9.4, 3.2, 2.8 Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 16.4, 17.5, 18.5, 19.3, 30.3, 32.5, 34.2, 55.7, 61.9, 77.7, 114.9, 117.5, 140.8, 153.4; HRMS calculated for $\text{C}_{16}\text{H}_{27}\text{NO}_2$ $[\text{M}]^+$: 265.2042, found: 242.2036.

Diastereomeric ratio was determined by analytical HPLC: HPLC Pump, sample injector, and UV-detector: Agilent Series 1100; Column: Macherey-Nagel, ET 125/2 Nucleosil, 120-5 C_{18} ; Flow: 0.3 mL/min, MeOH/ H_2O = 76:24; t_R for (*anti*)-isomer = 2.58 min and t_R for (*syn*)-

¹ M. S. Batra, F. J. Aguilar, E. Brunet, *Tetrahedron* **1994**, 50, 8169-8184.

isomer = 3.24. Identity of (*anti*)-isomer and (*syn*)-isomer was confirmed by isolation and complete characterization (see above / below).

(*anti*)-5-(4-Methoxy-phenylamino)-2,6-dimethyl-heptan-3-ol (10)

1H NMR (600 MHz, $CDCl_3$) δ 0.86 (d, J = 6.8 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H), 1.42 (ddd, J = 14.4 Hz, J = 10.2 Hz, J = 2.3 Hz, 1H), 1.62 (ddd, J = 14.4 Hz, J = 9.1 Hz, J = 2.6 Hz, 1H), 1.67 (sept, J = 6.8 Hz, 1H), 1.91 (sept d, J = 6.8 Hz, J = 5.2 Hz, J = 2.6 Hz, 1H), 3.45 (ddd, J = 10.1 Hz, J = 4.4 Hz, J = 2.8 Hz, 1H), 3.54 (ddd, J = 8.8 Hz, J = 6.0 Hz, J = 2.3 Hz, 1H), 3.73 (s, 3H), 6.62 (dt, J = 8.7, 2.8 Hz, 2H), 6.75 (dt, J = 9.1, 2.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.7, 18.1, 18.8, 19.1, 31.3, 34.1, 34.7, 55.8, 56.7, 74.1, 115.1, 115.2, 142.5, 152.2; HRMS calculated for $C_{16}H_{27}NO_2$ $[M]^+$: 265.2042, found: 242.2038.

Diastereomeric ratio was determined by analytical HPLC: HPLC Pump, sample injector, and UV-detector: Agilent Series 1100; Column: Macherey-Nagel, ET 125/2 Nucleosil, 120-5 C_{18} ; Flow: 0.3 mL/min, MeOH/ H_2O = 76:24; t_R for (*anti*)-isomer = 2.58 min and t_R for (*syn*)-isomer = 3.24. Identity of (*anti*)-isomer and (*syn*)-isomer was confirmed by isolation and complete characterization (see above).

(*syn*)-4,6-Diisopropyl-3-(4-methoxy-phenyl)-[1,3]oxazinane

A solution of (*syn*)-5-(4-Methoxy-phenylamino)-2,6-dimethyl-heptan-3-ol (20.0 mg, 75.0 μ mol) in THF (1 mL) was treated with 30 μ L of aq. 35% formaldehyde and the resulting

mixture was stirred at room temperature for 22 h. Evaporation of the solvent *in vacuo* and purification of the residue by preparative TLC (petroleum ether/ethyl acetate = 15:1) gave the oxazine as a colorless oil (21.0 mg, 75 μ mol, quant).

^1H NMR (300 MHz, CDCl_3) δ 0.79 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 7.0 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H), 1.45 (ddd, J = 13.1, 11.2, 11.0 Hz, 1H) 1.58 (ddd, J = 13.1, 3.4, 2.6 Hz, 1H) 1.64-1.85 (m, 2H), 2.91 (ddd, J = 11.0, 5.2, 3.4 Hz, 1H), 3.22 (ddd, J = 11.2, 6.4, 2.6 Hz, 1H), 3.77 (s, 3H), 4.34 (d, J = 8.9 Hz, 3H), 4.61 (d, J = 8.9 Hz, 3H), 6.8 (dt, J = 9.0, 2.8 Hz, 2H), 7.16 (dt, J = 8.9, 2.8 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) 16.4, 18.4, 18.5, 19.8, 27.3, 28.8, 33.2, 55.4, 64.2, 82.0, 85.7, 114.2, 126.6, 141.1, 156.7; HRMS calculated for $\text{C}_{17}\text{H}_{27}\text{NO}_2$ $[M]^+$: 277.2042, found: 277.2039.

(anti)-4,6-Diisopropyl-3-(4-methoxy-phenyl)-[1,3]oxazinane

A solution of (anti)-5-(4-Methoxy-phenylamino)-2,6-dimethyl-heptan-3-ol (10.0 mg, 37.5 μ mol) in THF (1 mL) was treated with 20 μ L of aq. 35% formaldehyde and the resulting mixture was stirred at room temperature for 22 h. Evaporation of the solvent *in vacuo* and purification of the residue by preparative TLC (petroleum ether/ethyl acetate = 15:1) gave the oxazine as a colorless oil (10.0 mg, 36.0 μ mol, 96%).

^1H NMR (600 MHz, CDCl_3) δ 0.87 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.42 Hz, 3H), 1.14 (d, J = 6.4 Hz, 3H), 1.45 (ddd, J = 13.6, 1.8, 1.8 Hz, 1H), 1.58-1.67 (m, 2H), 2.94 (dd, J = 10.8, 5.5 Hz, 1H), 3.44 (ddd, J = 11.9, 5.9, 1.5 Hz, 1H), 3.76 (s, 3H), 4.8 (d, J = 11.7 Hz, 1H), 4.87 (d, J = 11.7 Hz, 1H), 6.80 (dt, J = 8.7, 2.8 Hz, 2H), 7.11 (dt, J = 9.1, 2.8 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) 17.9, 18.0, 20.3, 21.1, 25.3, 26.7, 33.2, 55.6, 66.7, 76.2, 114.2, 121.7, 146.2, 154.2; HRMS calculated for $\text{C}_{17}\text{H}_{27}\text{NO}_2$ $[M]^+$: 277.2042, found: 277.2044.

6-Hydroxy-7-methyl-octan-4-one

Yield: 68%; ^1H NMR (300 MHz, CDCl_3) δ 0.89 (d, $J = 7.2$ Hz, 3H), 0.91 (d, $J = 7.4$ Hz, 3H), 1.59 (dd, $J = 14.7, 7.3$ Hz, 2H), 1.65 (sept d, $J = 6.8, 5.8$ Hz, 1H), 2.40 (t, $J = 7.4$ Hz, 2H), 2.45 (dd, $J = 17.1, 9.2$ Hz, 1H), 2.57 (dd, $J = 17.1, 2.8$ Hz, 1H), 3.78 (ddd, $J = 9.1$ Hz, 5.9, 2.9 Hz, 1H); ^{13}C NMR (75MHz, CDCl_3) δ 13.7, 17.1, 17.8, 33.1, 45.7, 46.0, 72.3, 212.7; MS (ESI) m/z 159 (100) $[\text{M}+\text{H}]^+$. The spectroscopic data were in agreement with those previously reported.²

(syn)-5-(4-Methoxy-phenylamino)-2-methyl-octan-3-ol (11)

^1H NMR (300 MHz, CDCl_3) δ 0.86 (t, $J = 7.2$ Hz, 3H), 0.91 (d, $J = 6.8$ Hz, 3H), 0.92 (d, $J = 6.8$ Hz, 3H), 1.20-1.60 (m, 5H), 1.65 (ddd, $J = 13.6, 6.8, 1.3$ Hz, 1H), 1.71 (ddd, $J = 14.4, 3.0, 2.0$ Hz, 1H), 3.41 (ddd, $J = 7.2, 7.2, 7.2, 4.0$ Hz, 1H), 3.64 (ddd, $J = 10.3, 5.2, 1.7$ Hz, 1H), 3.75 (s, 3H), 6.73 (dt, $J = 9.0, 2.5$ Hz, 2H), 6.78 (dt, $J = 9.0, 2.6$ Hz, 2H); ^{13}C NMR (75MHz, CDCl_3) δ 14.1, 17.7, 18.4, 19.0, 34.3, 36.7, 36.8, 55.7, 58.4, 77.3, 114.9, 118.9, 138.1, 154.6; HRMS calculated for $\text{C}_{16}\text{H}_{28}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 266.2126, found: 266.2120.

Diastereomeric ratio was determined by analytical HPLC: HPLC Pump, sample injector, and UV-detector: Agilent Series 1100; Column: Macherey-Nagel, ET 125/2 Nucleosil, 120-5 C_{18} ; Flow: 0.3 mL/min, $\text{CH}_3\text{CN}/\text{H}_2\text{O} = 55:45$; t_R for (*anti*)-isomer = 16.19 min and t_R for (*syn*)-isomer = 17.10. Identity of (*anti*)-isomer was confirmed by the UV-Spectrum [close similarity to (*syn*)-isomer] and by HPLC-MS measurements.

² S. N. Lewis, J. J. Miller, S. Winstein, *J. Org. Chem.* **1972**, 37, 1478.

5-Hydroxy-octan-3-one

Yield: 77%; ^1H NMR (300 MHz, CDCl_3) δ 0.91 (t, $J = 7.0$ Hz, 3H), 1.05 (t, $J = 7.4$ Hz, 3H), 1.28-1.54 (m, 4H), 2.4 (q, $J = 7.4$ Hz, 2H), 2.5 (dd, $J = 17.5, 8.9$ Hz, 1H), 2.59 (dd, $J = 17.5, 3.2$ Hz, 1H), 3.01 (brs, 1H), 4.03 (dddd, $J = 8.9, 7.8, 3.8, 3.2$ Hz, 1H); ^{13}C NMR (75MHz, CDCl_3) δ 7.6, 14.0, 18.7, 36.8, 38.6, 48.6, 67.4, 212.8; MS (EI) m/z 143 (67) $[\text{M}-\text{H}]^+$. The spectroscopic data were in agreement with those previously reported.³

(syn)-6-(4-Methoxy-phenylamino)-octan-4-ol (12)

^1H NMR (300 MHz, CDCl_3) δ 0.85 (t, $J = 7.4$ Hz, 3H), 0.93 (t, $J = 7.1$ Hz, 3H), 1.31-1.62 (m, 7H), 1.70 (ddd, $J = 14.1, 2.8, 2.6$ Hz, 1H), 3.39 (dddd, $J = 7.2, 7.2, 7.2, 4.0$ Hz, 1H), 3.74 (s, 3H), 3.87 (dddd, $J = 7.8, 7.0, 7.0, 3.0$ Hz, 1H), 6.68 (ddd, $J = 8.9, 3.0, 2.7$ Hz, 2H), 6.77 (ddd, $J = 8.9, 3.0, 2.8$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 9.7, 14.2, 18.7, 27.7, 40.4, 55.7, 58.1, 72.5, 114.8, 117.6, 140.4, 153.5; HRMS calculated for $\text{C}_{15}\text{H}_{26}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 252.1962, found: 252.1964.

Diastereomeric ratio was determined by analytical HPLC: HPLC Pump, sample injector, and UV-detector: Agilent Series 1100; Column: Macherey-Nagel, ET 125/2 Nucleosil, 120-5 C_{18} ; Flow: 0.3 mL/min, MeOH/ H_2O = 67:33; t_R for (*anti*)-isomer = 6.46 min and t_R for (*syn*)-isomer = 7.43. Identity of (*anti*)-isomer was confirmed by the UV-Spectrum [close similarity to (*syn*)-isomer] and by HPLC-MS measurements.

³ F. Gaudemar-bardone, M. Gaudemar, *J. Organomet. Chem.* **1976**, 104, 281.

5-Hydroxy-6-methyl-heptan-3-one

Yield: 87%; 1H NMR (300 MHz, $CDCl_3$) δ 0.83 (d, $J = 7.2$ Hz, 3H), 0.86 (d, $J = 6.8$ Hz, 3H), 0.99 (t, $J = 7.5$ Hz, 3H), 1.60 (sept d, $J = 6.7, 6.0$ Hz, 1H), 2.38 (q, $J = 7.3$ Hz, 1H), 2.40 (dd, $J = 17.3, 9.3$ Hz, 1H), 2.51 (dd, $J = 17.3, 2.8$ Hz, 1H), 3.03 (d, $J = 3.8$ Hz, 1H), 3.74 (dddd, $J = 9.3, 5.7$ Hz, $J = 3.8, 2.8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.4, 17.6, 18.2, 33.0, 36.7, 45.6, 72.2, 212.7; MS (ESI) m/z 145 (100) $[M+H]^+$. The spectroscopic data were in agreement with those previously reported.⁴

(syn)-5-(4-Methoxy-phenylamino)-2-methyl-heptan-3-ol (13)

1H NMR (300 MHz, CD_3OD) δ 0.95 (t, $J = 7.4$ Hz, 3H), 0.95 (d, $J = 6.8$ Hz, 3H), 0.96 (d, $J = 6.4$ Hz, 3H), 1.47-1.78 (m, 5 H), 3.38-3.49 (tdd, $J = 6.4, 5.8, 5.8$ Hz, 1H), 3.57 (ddd, $J = 9.5, 5.2, 3.2$ Hz, 1H), 3.75 (s, 3 H), 6.73 (dt, $J = 9.2, 2.7$ Hz, 2 H), 6.79 (dt, $J = 9.2, 2.7$ Hz, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 10.1, 17.8, 19.0, 27.9, 35.3, 38.4, 56.2, 76.7, 115.8, 117.3, 143.4, 153.9; HRMS calculated for $C_{15}H_{26}NO_2$ $[M+H]^+$: 252.1964, found: 252.1960.

Diastereomeric ratio was determined by analytical HPLC: HPLC Pump, sample injector, and UV-detector: Agilent Series 1100; Column: Macherey-Nagel, ET 125/2 Nucleosil, 120-5 C_{18} ; Flow: 0.3 mL/min, MeOH/ H_2O = 67:33; t_R for (*anti*)-isomer = 5.53 min and t_R for (*syn*)-isomer = 6.33. Identity of (*anti*)-isomer was confirmed by the UV-Spectrum [close similarity to (*syn*)-isomer] and by HPLC-MS measurements.

⁴ G. P. Luke, J. Morris, *J. Org. Chem.* **1995**, 60, 3013.

5-Hydroxy-2-methyl-tridecan-3-one (14)

$C_{14}H_{28}O_2$
Exact Mass: 228,2089
Mol. Wt.: 228,3709

Yield: 77%; 1H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 6.6 Hz, 3H), 1.09 (d, J = 7.0 Hz, 6H), 1.21-1.54 (m, 14H), 2.51 (dd, J = 17.7, 8.9 Hz, 1H), 2.57 (sept, J = 7.0 Hz, 1H), 2.63 (dd, J = 17.7, 3.0 Hz, 1H), 3.08 (d, J = 3.4 Hz, 1H), 3.95-4.05 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 18.0, 22.7, 25.5, 29.3, 29.6, 29.6, 31.9, 36.5, 41.5, 64.6, 67.7, 216.2; HRMS calculated for $C_{16}H_{31}NO_2Na$ $[M+Na+CH_3CN]^+$: 292.2252, found: 292.2255.

(syn)-3-(4-Methoxy-phenylamino)-2-methyl-tridecan-5-ol (14)

$C_{21}H_{37}NO_2$
Exact Mass: 335,2824
Mol. Wt.: 335,524

1H NMR (400 MHz, $CDCl_3$) δ 0.81 (d, J = 7.1 Hz, 3H), 0.87 (t, J = 6.6 Hz, 3H), 0.89 (d, J = 7.12 Hz, 3H), 1.23 - 1.59 (m, 15 H), 1.63 (ddd, J = 14.2, 2.3, 2.3 Hz, 1H), 1.92 (sept d, J = 6.6, 3.60 Hz, 1 H), 3.35 (ddd, J =11.06, 2.92, 2.80 Hz, 2H), 3.74 (s, 3H), 3.79-3.88 (m, 2H), 6.68 (dt, J = 9.1, 3.0 Hz, 2H), 6.76 (dt, J = 8.7, 2.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 16.3, 19.4, 22.7, 25.5, 29.3, 29.6, 29.8, 30.2, 31.9, 35.9, 38.3, 55.7, 61.8, 73.0, 114.9, 117.5, 140.8, 153.4; HRMS calculated for $C_{21}H_{38}NO_2$ $[M+H]^+$: 336.2903, found: 336.2902.

Diastereomeric ratio was determined by analytical HPLC: HPLC Pump, sample injector, and UV-detector: Agilent Series 1100; Column: Macherey-Nagel, ET 125/2 Nucleosil, 120-5 C_{18} ; Flow: 0.3 mL/min, MeOH/ H_2O = 67:33; t_R for (*anti*)-isomer = 13.98 min and t_R for (*syn*)-isomer = 15.91. Identity of (*anti*)-isomer was confirmed by the UV-Spectrum [close similarity to (*syn*)-isomer] and by HPLC-MS measurements.

6-Hydroxy-nonan-4-one

^1H NMR Yield: 67%; (300 MHz, CDCl_3) δ 0.90 (t, $J = 7.4$ Hz, 3H), 0.91 (t, $J = 6.7$ Hz, 3H), 1.27-1.66 (m, 6H), 2.39 (t, $J = 7.4$ Hz, 2H), 2.47 (dd, $J = 17.5, 8.9$ Hz, 1H), 2.57 (dd, $J = 17.50, 3.0$ Hz, 1H), 3.03 (d, $J = 2.6$ Hz, 1H), 3.95-4.06 (m, 1H); ^{13}C NMR (75MHz, CDCl_3) δ 13.7, 14.0, 17.1, 18.7, 38.6, 45.6, 49.0, 67.4, 212.5; MS (EI) m/z 157 (23) $[\text{M}-\text{H}^+]$. The spectroscopic data were in agreement with those previously reported.⁵

(syn)-6-(4-Methoxy-phenylamino)-nonan-4-ol (15)

^1H NMR (300 MHz, CDCl_3) δ 0.85 (t, $J = 7.1$ Hz, 3H), 0.92 (t, $J = 7.1$ Hz, 3H), 1.23-1.57 (m, 9H), 1.7 (ddd, $J = 14.3, 3.1, 2.0$ Hz, 1H), 3.38-3.47 (m, $J = 7.2, 7.2, 7.2, 3.6$ Hz, 1H), 3.74 (s, 3H) 3.83-3.91 (m, 1H), 6.68 (dt, $J = 9.2, 3.1, 2.9$ Hz, 2H), 6.77 (ddd, $J = 9.2, 3.1, 2.9$ Hz, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 14.1, 14.2, 18.7, 18.9, 37.8, 40.4, 41.1, 55.7, 56.7, 72.4, 114.8, 117.4, 140.7, 153.4; HRMS calculated for $\text{C}_{16}\text{H}_{28}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 266.2128, found: 266.2120.

Diastereomeric ratio was determined by analytical HPLC: HPLC Pump, sample injector, and UV-detector: Agilent Series 1100; Column: Macherey-Nagel, ET 125/2 Nucleosil, 120-5 C_{18} ; Flow: 0.3 mL/min, MeOH/ H_2O = 67:33; t_R for (*anti*)-isomer = 10.44 min and t_R for (*syn*)-isomer = 12.17. Identity of (*anti*)-isomer was confirmed by the UV-Spectrum [close similarity to (*syn*)-isomer] and by HPLC-MS measurements.

⁵ G. Stork, G. A. Kraus, G. A. Garcia, *J. Org. Chem.* **1976**, 39, 3459.

1-Hydroxy-4-methyl-1-phenyl-pentan-3-one

$C_{12}H_{16}O_2$
Exact Mass: 192,115
Mol. Wt.: 192,2542

Yield: 87%; 1H NMR (400 MHz, $CDCl_3$) δ 1.08 (d, J = 6.6 Hz, 3H), 1.08 (d, J = 7.1 Hz, 3H), 2.56 (sept, J = 7.1 Hz, 1H), 2.80 (dd, J = 17.3, 4.1 Hz, 1H), 2.87 (dd, J = 17.3, 8.7 Hz, 1H), 5.13 (dd, J = 8.6, 3.6 Hz, 1H), 7.23-7.28 (m, 1H), 7.30-7.36 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 41.5, 48.8, 70.0, 125.6, 127.6, 128.5, 143.1, 215.0; MS (ESI) m/z 256 (100) $[M+Na+CH_3CN]^+$. The spectroscopic data were in agreement with those previously reported.⁶

(syn)-3-(4-Methoxy-phenylamino)-4-methyl-1-phenyl-pentan-1-ol (16)

$C_{19}H_{25}NO_2$
Exact Mass: 299,1885
Mol. Wt.: 299,4073

1H NMR (300 MHz, $CDCl_3$) δ 0.81 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 7.0 Hz, 3H), 1.63 (ddd, J = 14.4, 10.7, 9.6 Hz, 1H), 1.86 (ddd, J = 14.5, 3.0, 3.0 Hz, 1H), 1.95 (sept d, J = 7.0, 3.4 Hz, 1H), 3.44 (d, J = 9.4 Hz, 1H), 3.76 (s, 3H), 4.95 (dd, J = 9.4, 3.4 Hz, 1H), 6.71 (dt, J = 9.0, 2.9 Hz, 2H), 6.80 (dt, J = 9.0, 3.2 Hz, 2H), 7.22-7.30 (m, 1H), 7.30-7.43 (m, 4H); ^{13}C NMR (75 MHz, CD_3OD) δ 16.2, 19.3, 30.2, 38.8, 55.7, 61.4, 75.2, 114.9, 117.5, 125.8, 127.4, 128.4, 140.6, 144.9, 153.4; HRMS calculated for $C_{19}H_{26}NO_2$: 300,1964 $[M+H]^+$, found: 300.1967.

Diastereomeric ratio was determined using 1H -NMR analysis by integration of the OMe-Signals of the PMP-group.

⁶ H.X. Wei, R. L. Jasoni, H. Shao, J. Hu, P. W. Pare, *Tetrahedron* **2004**, *60*, 11829.

1-Cyclohexyl-3-hydroxy-4-methyl-pentan-1-one

$C_{12}H_{22}O_2$
Exact Mass: 198,162
Mol. Wt.: 198,3019

Yield: 87%; 1H NMR (400 MHz, $CDCl_3$) δ 0.86 (d, $J = 7.1$ Hz, 3H), 0.89 (d, $J = 6.7$ Hz, 3H), 1.11-1.35 (m, 5H), 1.56-1.67 (m, 2H), 1.69-1.85 (m, 4H), 2.30 (tt, $J = 10.7, 3.6$, 1H), 2.45 (dd, $J = 17.3, 9.2$, 1H), 2.57 (dd, $J = 17.3, 2.5$, 1H), 3.07 (d, $J = 3.6$ Hz, 1H), 3.70-3.76 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 18.4, 25.5, 25.8, 28.3, 33.0, 43.9, 51.5, 72.3, 215.6; HRMS calculated for $C_{14}H_{25}NO_2Na$ $[M+CH_3CN+Na]^+$: 262.1783, found: 262.1786.

(*syn*)-1-Cyclohexyl-1-(4-methoxy-phenylamino)-4-methyl-pentan-3-ol (17)

$C_{19}H_{31}NO_2$
Exact Mass: 305,2355
Mol. Wt.: 305,4549

1H NMR (300 MHz, $CDCl_3$) δ 0.92 (d, $J = 6.6$ Hz, 3H), 0.93 (d, $J = 6.8$ Hz, 3H), 0.98-1.78 (m, 14 H), 3.31 (ddd, $J = 10.7, 2.5, 2.5$ Hz, 1H), 3.61 (ddd, $J = 10.0, 5.1, 1.9$ Hz, 1H), 3.75 (s, 3H), 6.71 (dt, $J = 9.0, 3.0$ Hz, 2H), 6.78 (dt, $J = 9.0, 3.0$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 18.5, 26.3, 26.5, 26.6, 27.4, 30.0, 41.1, 55.7, 62.4, 77.9, 114.9, 117.9, 140.0, 153.8; HRMS calculated for $C_{19}H_{32}NO_2$ $[M+H]^+$: 306.2433, found: 306.2431.

Diastereomeric ratio was determined by analytical HPLC: HPLC Pump, sample injector, and UV-detector: Agilent Series 1100; Column: Macherey-Nagel, ET 125/2 Nucleosil, 120-5 C_{18} ; Flow: 0.3 mL/min, MeOH/ H_2O = 67:33; t_R for (*anti*)-isomer = 5.32 min and t_R for (*syn*)-isomer = 6.28. Identity of (*anti*)-isomer was confirmed by the UV-Spectrum [close similarity to (*syn*)-isomer] and by HPLC-MS measurements.

1-Furan-2-yl-3-hydroxy-4-methyl-pentan-1-one

1H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H), 1.77 (sept d, J = 6.7, 5.9 Hz, 1H), 2.88 (dd, J = 16.8, 9.4 Hz, 1H), 2.96 (d, J = 3.58 Hz, 1H), 3.02 (dd, J = 16.8, 2.6 Hz, 1H), 3.91-3.99 (m, 1H), 6.54 (dd, J = 3.6, 1.7 Hz, 1H), 7.21 (dd, J = 3.6, 0.8 Hz, 1H), 7.58 (dd, J = 1.7, 0.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8, 18.5, 33.3, 41.9, 72.5, 112.4, 117.6, 146.7, 152.8, 190.0; MS (ESI) m/z 246 (100) $[M+Na+CH_3CN]^+$. The spectroscopic data were in agreement with those previously reported.⁷

1-Furan-2-yl-1-(4-methoxy-phenylamino)-4-methyl-pentan-3-ol (18)

Yield: 84%; 1H NMR (300 MHz, CD_3OD) δ 0.96 (d, J = 7.0 Hz, 6H), 1.69 (sept d, J = 7.0, 5.5 Hz, 1 H), 1.88-2.00 (m, 2H), 3.65 (ddd, J = 9.0, 5.3, 3.2 Hz, 3H), 3.72 (s, 3H), 4.70 (dd, J = 9.2, 4.1 Hz, 1H), 6.13 (d, J = 3.2 Hz, 1H), 6.29 (dd, J = 3.2, 1.9 Hz, 3H), 6.7 (dt, J = 9.2, 3.1 Hz, 2H), 6.7 (dt, J = 9.2, 3.1 Hz, 2H), 7.38 (dd, J = 1.9, 0.9 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 17.8, 19.2, 35.2, 40.6, 51.3, 56.2, 73.9, 106.4, 110.9, 115.6, 116.4, 142.3, 143.7, 153.5, 159.0; HRMS calculated for $C_{17}H_{24}NO_3$: 290.1756 $[M+H]^+$, found: 290.1761.

Diastereomeric ratio was determined by analytical HPLC: HPLC Pump, sample injector, and UV-detector: Agilent Series 1100; Column: Macherey-Nagel, ET 125/2 Nucleosil, 120-5 C_{18} ; Flow: 0.3 mL/min, CH_3CN/H_2O = 55:45; t_R for (*anti*)-isomer = 14.43 min and t_R for (*syn*)-isomer = 15.55. Identity of (*anti*)-isomer was confirmed by the UV-Spectrum [close similarity to (*syn*)-isomer] and by HPLC-MS measurements.

⁷ T.-P. Loh, X.-R. Li, *Tetrahedron* **1999**, 55, 10789.

3-Hydroxy-4-methyl-1-phenyl-pentan-1-one

C₁₂H₁₆O₂
Exact Mass: 192,115
Mol. Wt.: 192,2542

¹H NMR (300 MHz, CDCl₃) δ 0.98 (d, *J* = 6.6 Hz, 3H), 1.00 (d, *J* = 6.6 Hz, 3H), 1.80 (sept d, *J* = 6.6, 5.6 Hz, 1H), 3.02 (dd, *J* = 17.3, 9.2 Hz, 1H), 3.12-3.14 (m, 1H), 3.16 (dd, *J* = 17.3, 2.6 Hz, 1H), 3.95-4.02 (m, 1H), 7.43-7.49 (m, 2H), 7.57 (tt, *J* = 7.2, 1.3 Hz, 1 H), 7.93-7.97 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 17.9, 18.6, 33.2, 42.0, 72.5, 128.7, 133.5, 137.0, 201.3; MS (ES) *m/z* 193 (100) [M+H]⁺. The spectroscopic data were in agreement with those previously reported.⁸

(syn)-1-(4-Methoxy-phenylamino)-4-methyl-1-phenyl-pentan-3-ol (19)

¹H NMR (300 MHz, CDCl₃) δ 0.91 (d, *J* = 6.8 Hz, 3H), 1.66 (sept d, *J* = 6.8, 4.9 Hz, 1H), 1.80-1.88 (m, 2H), 3.62 (ddd, *J* = 6.8, 5.1, 5.1 Hz, 1H), 3.68 (s, 3H), 4.42 (dd, *J* = 7.4, 6.5 Hz, 1H), 6.55 (dt, *J* = 9.0, 2.9 Hz, 2H), 6.67 (dt, *J* = 9.0, 2.9 Hz, 2H), 7.19-7.24 (m, 1H), 7.27-7.33 (m, 5H); ¹³C NMR (75MHz, CDCl₃) δ 17.3, 18.4, 34.4, 42.0, 55.7, 60.5, 73.8, 114.7, 116.5, 126.2, 127.1, 128.7, 140.9, 144.1, 152.9; HRMS calculated for C₁₉H₂₅NO₂ [M]⁺: 299.1885, found: 299.1883.

Diastereomeric ratio was determined by analytical HPLC: Hewlett Packard HPLC Pump Series 1050, Syringe Loading sample injector, UV detector: Techlab R SPD6AV, detection at 254 nm. Column: Chiralcel OD-H (Daicel Chem. Ind. Ltd., 4.6 mm x 250 mm, 0.5 mL/min), hexane/*i*-PrOH = 90:10: *t_R* for (*anti*)-isomers = 17.17 and 18.28 min and *t_R* for (*syn*)-isomers = 20.92 and 22.88. Identity of (*anti*)-isomers was confirmed by HPLC-MS measurements.

⁸ Y. Tanabe, N. Matsumoto, T. Higashi, T. Misaki, T. Itoh, M. Yamamoto, K. Mitarai, Y. Nishii, *Tetrahedron* **2002**, 58, 8269.

((1S,2S,4S)-4-Amino-1-benzyl-2-hydroxy-5-phenyl-pentyl)-carbamic acid *tert*-butyl ester (23)

To a cooled (0 °C) solution of (+)Ipc₂BCl [(+)-DIPCl, 157 mg, 490 μmol) in anhydrous Et₂O (3 mL) was added Et₃N (68.3 μL, 490 μmol), followed phenylacetone (43.7 mg, 326 μmol). The white suspension was stirred for 3 hours at 0 °C before cooling to -78°C, and BOC-protected aldehyde **21** (89.3 mg, 358 μmol) in Et₂O (1 mL) was added dropwise. The reaction mixture was allowed to warm to -50 °C over 2 hours and then stirred at 0°C for 1 hour. The reaction was quenched by sequential addition of methanol (10 mL), pH7 buffer, (4.2 mL) and 30% aq H₂O₂ (1 mL) and the biphasic system was stirred vigorously at 0°C for 10 minutes and then at room temperature for 1 hour. The mixture was poured into water and extracted with EtOAc/petroleum ether (1:1 v/v). (5x5 mL) The combined organic extracts were washed with H₂O, dried (MgSO₄), and concentrated *in vacuo*. The resulting oil was dissolved in acetonitrile (2 mL) and treated with *p*-anisidine (**8**, 652 μmol, 80.2 mg) and titanium(IV) isopropoxide (456 μmol, 130 mg, 143 μL) and was stirred under argon at -20 °C for 1 h. At this temperature, a solution of polymethyl-hydrosiloxane (43.7 mg, 720 μmol) in acetonitrile (1 mL) was added and the resulting mixture was stirred for 48 h. The reaction mixture was treated with 2 mL aq. NaOH solution (1M) and under stirring warmed to room temperature. The solution was thoroughly extracted with ether. The combined organic phases were washed with brine, dried (MgSO₄) and the solvent evaporated *in vacuo*. The oily residue was dissolved into a mixture of MeOH/H₂O (20 mL, 4:1) and cooled to 0 °C; CAN (cerium ammonium nitrate) (1.05 g, 191 mmol) was added in one portion and the resulting reaction system was stirred for 6 h at the same temperature. Water was added and the solution was washed with CH₂Cl₂. The aqueous solution was made alkaline by adding 1 N NaOH, and then extracted with ethyl acetate. The combined organic solution was washed with brine and dried over MgSO₄. The solvent was removed under vacuum, and the residue was purified through silica gel column chromatography (petroleum ether / ethyl acetate = 4:1) afforded hydroxylamine **24** as an amorphous solid (58.8 mg, 182 μmol, 56%).

$[\alpha]_D^{22} = -20$ ($c = 0.20$, MeOH); ¹H NMR (300 MHz, CDCl₃) δ 1.31 (ddt, $J = 14.3, 8.9, 8.5$ Hz, 1H), 1.42 (s, 9H), 1.43 (m, 1H), 2.48 (dd, $J = 13.6, 8.2$ Hz, 1H), 2.80 (dd, $J = 13.6, 4.9$ Hz,

1H), 2.86 (d, 2H, $J = 7.5$ Hz), 3.06 (ddt, 8.9, 3.2, 7.5 Hz, 1H), 3.66 (m, 1H), 3.78 (m, 1H), 7.06-7.32 (m, 10H); ^{13}C NMR (75MHz, CDCl_3) δ 28.4, 38.8, 38.9, 46.8, 53.9, 56.3, 71.4, 78.9, 126.0, 126.6, 128.3, 128.6, 129.0, 129.3, 129.5, 129.6, 137.7, 138.8, 155.9; MS (ES) m/z 323 (100) $[\text{M}+\text{H}]^+$. The spectroscopic data were in agreement with those previously reported.⁹

⁹ F. Benedetti, F. Berti, S. Norbedo, *J. Org. Chem.* **2002**, 67, 8635.

HPLC-Traces

RT (min)	FlAche mAU*sec
6.46	833.4
7.43	7503.3

RT (min)	FlAche mAU*sec
5.53	456.6
6.33	5025.4

RT (min)	Fläche mAU*sec
13.98	825.4
15.91	5093.1

RT (min)	Fläche mAU*sec
10.44	825.4
12.17	6070.7

RT (min)	Fläche mAU*sec
5.32	393.6
6.20	3409.2
17.62	577.0

RT (min)	Fläche mAU*sec
14.43	234.1
15.55	1467.5

CHROMATOGRAM 1 MEMORIZED

CHROMATOPAC C-R3A
SAMPLE NO 0
REPORT NO 4399

FILE 8
METHOD 421

PKNO	TIME	AREA	HK	IDNO	CONC	NAME
1	17.172				5.5649	
2	18.283				6.0734	
3	20.922				44.1942	
4	22.878				44.1676	
TOTAL					100

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