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Supporting Information

On a Chemoenzymatic Desymmetrization/Ring Expansion Strategy Towards Functionalized *N*-Heterocycles

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General remarks

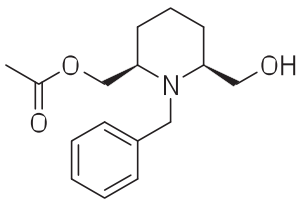
All moisture or air sensitive reactions were performed under argon atmosphere in oven-dried glassware. Dry tetrahydrofuran was freshly distilled from sodium and benzophenon. Anhydrous dichloromethan was freshly distilled from calcium hydride. Commercially available reagents were used without further purification. Biocatalysts were obtained from: CALA: Lipase A, *Candida antarctica*, CLEA, Sigma; CALB: Lipase acrylic resin from *Candida antarctica*, Novozym 435, Novo Nordisk A/S; CRL: Lipase from *Candida rugosa*, Amano AYS, Amano Enzyme; TLL: Lipase from *Thermomyces lanuginosus*, immobilized on Immobead 150, Sigma; PCL: Lipase from *Pseudomonas cepacia*, immobilized on Immobead 150, Sigma; PPL: lipase from porcine pancreas, MP Biomedicals; PFL: lipase from *Pseudomonas fluorescens*, immobilized on Immobead 150, Sigma; MML: lipase from *Mucor miehei*, Lipozyme IM, Novo Nordisk A/S. All products were purified by column chromatography over silica gel (Macherey-Nagel MN-Kieselgel 60 (40-60 μm, 240-400 mesh)). Analytical thin-layer chromatography was performed on Macherey-Nagel precoated silica gel plates (ALUGRAMM Sil G/UV254), visualization of the compounds was achieved by UV light (254 nm), $KMnO_4$-solution or iodine. ^{1}H- and ^{13}C-NMR-spectra were recorded on a Bruker Avance 300 spectrometer at room temperature at 300 and 75 MHz respectively. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane, using residual $CHCl_3$ (7.26 ppm and 77.1 ppm, respectively) or D_2O (4.79 ppm) as internal standard. Infrared-spectra were recorded on a Shimadzu IRAffinity-1 FT-IR-spectrometer, absorption bands are reported in wave numbers [cm^{-1}]. High resolution mass spectrometry was performed on a Finnigan MAT 900 S. High performance liquid chromatography was performed on a Merck D-7000 with a Merck L-4500 PDA-detector using an analytical Daicel Chiralpak column (250 mm x 4.6 mm). Optical rotations were measured on a Perkin-Elmer 343plus.

Procedures and analytical data of the compounds

General procedure 1 for the desymmetrization of *meso*-diols 1a-c

meso-Diol **1a-c** (1 eq) was dissolved in dry toluene (0.1 M), vinyl acetate (10 eq) and Lipozyme IM (10 mg/mmol) were added and incubated for 16 h at 35 °C. The mixture was filtered through cotton, concentrated in vacuo and the crude product was purified by column chromatography (SiO_2, cyclohexane/ethyl acetate 4/1).

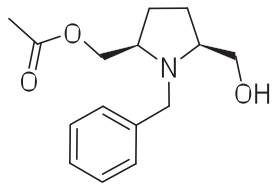
(2*R*,5*S*)-*N*-Benzyl-2-(acetoxymethyl)-5-(hydroxymethyl)piperidine (2a)



(2*R*,6*S*)-**2a**

Starting from *meso*-diol **1a**,[1] following the general procedure 1 monoacetate **2a** (0.61 g, 2.19 mmol, 85% yield) was obtained as yellow oil. $[\alpha]^{20}_{D}$: +13.3 (c 0.95, $CHCl_3$), 99% *ee*. R_f (cyclohexane/ethyl acetate 3/1): 0.15. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ [ppm] = 7.40-7.23 (m, 5H), 4.14 (dd, ^2J = 12.6 Hz, ^3J = 5.7 Hz, 1H), 4.01 (dd, ^2J = 12.6 Hz, ^3J = 6.2 Hz, 1H), 3.92 (d, ^2J = 15.8 Hz, 1H), 3.81-3.74 (d, ^2J = 15.8 Hz, 1H), 3.55 (dd, ^2J = 11.0 Hz, ^3J = 4.7 Hz, 1H), 3.38 (dd, ^2J = 12.6 Hz, ^3J = 6.2 Hz, 1H), 2.95-2.85 (m, 1H), 2.80-2.70 (m, 1H), 2.00 (s, 3H), 1.80-1.70 (m, 2H), 1.65-1.55 (m, 2H), 1.45-1.35 (m, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ = 170.1, 141.0, 128.6, 127.6, 127.0, 67.0, 62.6, 62.3, 60.0, 55.8, 26.2, 25.6, 21.2, 20.9. **FT-IR** (neat, ATR): ν [cm^{-1}] = 3512 (br), 2933 (m), 2858 (w), 1735 (s), 1450 (m), 1367 (m), 1263 (s), 1045 (s), 1026 (s), 958 (w), 729 (s), 698 (s), 603 (m). **Anal.** calcd (%) for $C_{16}H_{23}NO_3$: C 69.29, H 8.36, N 5.05; found: C 69.12, H 8.35, N 5.04. **HPLC**: *Chiralpak AD-H*, *n*-hexane/ *i*-PrOH 95/5, 1 ml/min, 220 nm: t_R (2*S*,5*R*)-**2a** = 12.3 min, t_R (2*R*,5*S*)-**2a** = 14.2 min.

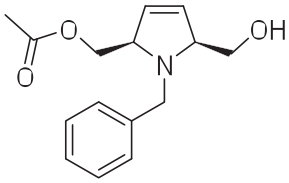
(2*R*,5*S*)-*N*-Benzyl-2-(acetoxymethyl)-5-(hydroxymethyl)pyrrolidine (2b)



(2*R*,5*S*)-**2b**

Starting from diol **1b**,[2] following the general procedure 1, monoacetate **2b** (1.97 g, 7.48 mmol, 74% yield) was obtained as yellow oil. $[\alpha]^{20}_{D}$: +17.2 (c 0.5, $CHCl_3$), 99% *ee*. R_f (cyclohexane/ethyl acetate 3/1): 0.16. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ [ppm] = 7.20-7.36 (m, 5H), 3.93 (dd, ^2J = 11.0 Hz, ^3J = 5.1 Hz, 1H), 3.88-3.75 (m, 3H), 3.40-3.34 (m, 2H), 3.21-3.25 (m, 1H), 3.05-2.98 (m, 1H), 2.01 (s, 3H), 1.94-1.79 (m, 3H), 1.69-1.59 (m, 1H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ = 170.0, 139.2, 128.9, 128.5, 127.4, 67.0, 66.0, 63.1, 62.2, 58.6, 27.8, 27.0, 20.9. **FT-IR** (neat, ATR): ν [cm^{-1}] = 3408 (br), 2949 (w), 2873 (w), 2818 (w), 1735 (s), 1454 (w), 1365 (m), 1228 (s), 1074 (m), 1029 (s), 968 (m), 750 (m), 700 (s), 605 (m). **Anal.** calcd (%) for $C_{15}H_{21}NO_3$: C 68.42, H 8.04, N 5.32; found: C 68.14, H 7.93, N 5.44. **HPLC**: *Chiralpak AD-H*, *n*-hexane/*i*-PrOH 95/5, 1 ml/min, 220 nm: t_R (2*S*,5*R*)-**2b** = 12.9 min, t_R (2*R*,5*S*)-**2b** = 13.9 min.

(2*R*,5*S*)-*N*-Benzyl-2-(acetoxymethyl)-5-(hydroxymethyl)-2,5-dihydropyrrole (2c)



(2*R*,5*S*)-**2c**

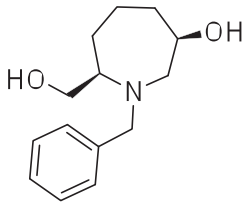
Starting from diol **1c**,[3] following the general procedure 1 but incubated at 22 °C, monoacetate **2c** (0.32 g, 1.22 mmol, 67% yield) was obtained as yellow oil. $[\alpha]^{20}_{D}$: +44.0 (c 0.49, $CHCl_3$), 95% *ee*. R_f (cyclohexane/ethyl acetate 3/1): 0.16. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ [ppm] = 7.40-7.23 (m, 5H), 5.70 (m, 2H), 4.19 (dd, ^2J = 11.0 Hz, ^3J = 3.6 Hz, 1H), 4.05-3.87 (m, 4H), 3.74 (dd, ^2J = 10.7 Hz, ^3J = 4.1 Hz, 1H), 3.40 (d, ^2J = 10.7 Hz, 1H), 3.23 (dd, ^2J = 10.7 Hz, ^3J = 2.9 Hz, 1H), 2.87 (s, 1H), 2.04 (s, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ = 171.0, 138.8, 130.9, 128.8, 128.7, 127.2, 126.3, 72.9, 70.6, 66.2, 62.3, 58.6, 20.8. **FT-IR** (neat, ATR): ν [cm^{-1}] = 3440 (br), 2911 (w), 2850 (w), 2800 (w), 1735 (s), 1377 (m), 1365 (m), 1222 (s), 1128 (m), 1029 (s), 833 (w), 700 (s). **Anal.** calcd (%) for $C_{15}H_{19}NO_3$: C 68.94,

H 7.33, N 5.36; found: C 68.62, H 7.32, N 5.56. **HPLC**: *Chiralpak AD-H*, *n*-hexane/*i*-PrOH 95/5, 1 ml/min, 220 nm: t_R (2*S*,5*R*)-**2c** = 12.7 min, t_R (2*R*,5*S*)-**2c** = 14.5 min.

General procedure 2 for the trifluoroacetate-mediated ring expansion

To a stirred solution of monoacetate **2a** or **2b** (1.0 eq) in dry THF (1 M) at –78 °C was added dropwise trifluoroacetic anhydride (1.5 eq). After 2 h at –78 °C, triethylamine (3.0 eq) was added slowly and the reaction mixture was stirred for additional 15 min and then heated to reflux for 48 h. The resulting brown solution was concentrated in vacuo and then dissolved in methanol (0.2 M) followed by addition of aqueous NaOH (0.5 M, 5.0 eq.). After 2 h at room temperature the reaction mixture was saturated with NaCl and then extracted with ethyl acetate (3 x 10 ml/mmol). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography (CH_2Cl_2/MeOH 10/1) gave the corresponding diol **3a** or **3b**.

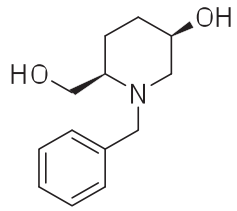
(2*R*,7*R*)-*N*-Benzyl-7-(hydroxymethyl)azepan-3-ol (3a)



(3*R*,7*R*)-**3a**

Following the general procedure 2 diol **3a** (42.3 mg, 0.18 mmol, 23% yield) was obtained as yellow oil. $[\alpha]^{20}_D$: +33.5 (c 0.90, $CHCl_3$). R_f (ethyl acetate): 0.28. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ [ppm] = 7.33-7.20 (m, 5H), 3.96 (d, ^2J = 14.4 Hz, 1H), 3.95-3.86 (m, 1H), 3.90 (d, ^2J = 14.5 Hz, 1H), 3.60-3.49 (m, 2H), 2.98-2.83 (m, 3H), 1.89-1.48 (m, 6H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ = 143.9, 128.9, 128.6, 127.5, 68.0, 63.6, 63.5, 58.8, 54.6, 37.5, 29.7, 21.3. **FT-IR** (neat, ATR): ν [cm^{-1}] = 3342 (br), 2929 (m), 2883 (m), 2856 (m), 1450 (m), 1097 (m), 1097 (m), 1045 (s), 1026 (s), 729 (s), 698 (s). **HRMS** (ESI): calcd for $C_{14}H_{21}NO_2$ $[M+H]^+$: 236.1650, found: 236.1650.

(3*R*,6*R*)-*N*-Benzyl-6-(hydroxymethyl)piperidin-3-ol (3b)



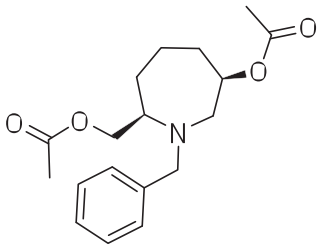
(3*R*,6*R*)-**3b**

Following the general procedure 2 piperidine **3b** (55.6 mg, 0.26 mmol, 65% yield) was obtained as yellow oil. $[\alpha]^{20}_{D}$: +28.7 (c 1.20, $CHCl_3$). R_f (ethyl acetate): 0.19. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ [ppm] = 7.33-7.20 (m, 5H), 4.18 (d, ^2J = 13.4 Hz, 1H), 3.94-3.85 (m, 2H), 3.66 (dd, ^2J = 11.4 Hz, ^3J = 4.3 Hz, 1H), 3.58 (d, ^2J = 13.4 Hz, 1H), 3.09 (s, 1H), 2.92 (dd, ^2J = 12.8 Hz, ^3J = 12.8 Hz, 1H), 2.63-252 (m, 1H), 2.42 (d, ^2J = 12.7 Hz, 1H), 2.05-1.90 (m, 1H), 1.85-1.74 (m, 1H), 1.70-1.53 (m, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ = 135.9, 129.2, 128.6, 127.7, 64.3, 62.4, 61.4, 57.7, 56.4, 30.1, 22.6. **FT-IR** (neat, ATR): ν [cm^{-1}] = 3325 (br), 2931 (m), 2887 (m), 2802 (m), 1674 (m), 1450 (m), 1116 (m), 1062 (m), 1043 (m), 1028 (m), 734 (s), 681 (s). **HRMS** (ESI): calcd for $C_{13}H_{19}NO_2$ *m/z* $[M+H]^+$: 222.1494, found: 222.1490.

General procedure 3 for the triflate-mediated ring expansion

Proton sponge (1,8-Bis-(dimethylamino)naphthalene, 1.3 eq) was dissolved in dry CH_2Cl_2 (0.1 M) and cooled to –20 °C. A solution of monoacetate (1 eq) in dry CH_2Cl_2 (0.1 M) was added dropwise to the reaction mixture and stirred for 30 min at –20 °C. Addition of trifluoromethanesulfonic anhydride (1.1 eq) causes a dark red colour. After 30 min, sodium acetate (3.0 eq) was added and the reaction mixture was stirred over night at –20 °C and then allowed to warm to room temperature. The solution was diluted with water (5 ml/mmol), extracted with CH_2Cl_2 (2 x 10 ml/mmol) and the combined organic layers were dried over $MgSO_4$. Purification by flash column chromatography with cyclohexane/ethyl acetate as eluent gave the corresponding diacetate **5a-c**.

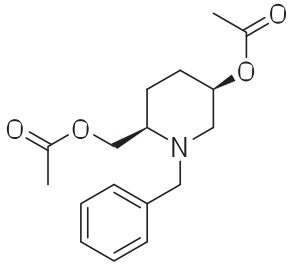
(3*R*,7*R*)-*N*-Benzyl-7-(acetoxymethyl)-3-acetoxyazepane (5a)



(3*R*,7*R*)-**5a**

Following the general procedure 3 diacetate **5a** (5.0 mg, 15.6 µmol, 8% yield) was obtained after purification by column chromatography (SiO_2, cyclohexane/ethyl acetate 9/1) as yellow oil. $[\alpha]^{20}_D$: +6.3 (c 0.49, $CHCl_3$). R_f (cyclohexane/ethyl acetate 3/1): 0.55. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ [ppm] = 7.34-7.21 (m, 5H), 4.82-4.72 (m, 1H), 4.03-3.95 (m, 2H), 3.84 (dd, ^2J = 10.8 Hz, ^3J = 6.5 Hz, 1H), 3.78 (d, ^2J = 14.7 Hz, 1H), 2.97-2.85 (m, 2H), 2.69 (d, ^2J = 14.6 Hz, 1H), 2.10-1.68 (m, 3H), 1.95 (s, 3H), 1.87 (s, 3H), 1.51-1.27 (m, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ = 171.2, 170.2, 140.1, 128.5, 128.2, 127.0, 71.9, 66.2, 60.1, 58.8, 52.0, 34.6, 30.8, 21.3, 21.2, 21.0. **FT-IR** (neat, ATR): ν [cm^{-1}] = 2930 (w), 2899 (w), 2800 (w), 1737 (s), 1685 (s), 1455 (w), 1372 (m), 1360 (m), 1228 (s), 1134 (m), 1104 (m), 1029 (m), 954 (m), 700 (s), 629 (s). **HRMS** (ESI): calcd for $C_{18}H_{25}NO_4$ *m/z* $[M+H]^+$: 320.1862, found: 320.1860.

(3*R*,6*R*)-*N*-Benzyl-6-(acetoxymethyl)-3-acetoxypiperidine (5b)

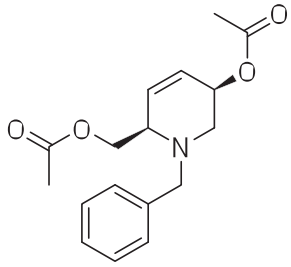


(3*R*,6*R*)-**5b**

Following the general procedure 3 diacetate **5b** (7.5 mg, 24.5 µmol, 12% yield) was obtained after purification by column chromatography (SiO_2, cyclohexane/ethyl acetate 4/1) as yellow oil. $[\alpha]^{20}_D$: +5.7 (c 0.51, $CHCl_3$). R_f (cyclohexane/ethyl acetate 3/1): 0.50. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ [ppm] = 7.34-7.21 (m, 5H), 4.92-4.83 (m, 1H), 4.39 (dd, ^2J = 11.7 Hz, ^3J = 5.4 Hz, 1H), 4.22 (dd, ^2J = 11.7 Hz, ^3J = 5.8 Hz, 1H), 3.89 (d, ^2J = 13.6 Hz, 1H), 3.68 (d, ^2J = 13.8 Hz, 1H), 3.15-3.08 (m, 1H), 2.73 (dd, ^2J = 11.1 Hz, ^3J = 6.5 Hz, 1H), 2.58 (dd, ^2J = 10.6

Hz, ^3J = 4.1 Hz, 1H), 2.09 (s, 3H), 2.04 (s, 3H), 1.90-1.75 (m, 4H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ = 171.1, 170.4, 140.0, 128.6, 128.5, 127.2, 72.0, 66.3, 60.1, 58.8, 52.1, 34.7, 30.9, 21.3, 21.0. **FT-IR** (neat, ATR): ν [cm^{-1}] = 2955 (br), 1736 (s), 1688 (s), 1456 (w), 1382 (m), 1365 (m), 1226 (s), 1105 (w), 1031 (s), 970 (w), 755 (w), 701 (m). **Anal.** calcd (%) for $C_{17}H_{23}NO_4$: C 66.86, H 7.59, N 4.59; found: C 66.77, H 7.63, N 4.97.

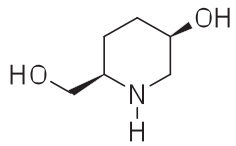
(3*R*,6*R*)-*N*-Benzyl-6-(acetoxymethyl)-3-acetoxy-1,2,3,6-tetrahydropyridine (5c)



(3*R*,6*R*)-**5c**

Following the general procedure 3 diacetate **5c** (27.0 mg, 89.0 µmol, 45% yield) was obtained after purification by column chromatography (SiO_2, cyclohexane/ethyl acetate 4/1) as yellow oil. **$[\alpha]^{20}_D$**: –15.5 (c 0.67, $CHCl_3$), **R_f** (cyclohexane/ethyl acetate 5/1): 0.21. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ [ppm] = 7.35-7.21 (m, 5H), 5.97-5.87 (m, 2H), 5.31-5.24 (m, 1H), 4.30 (dd, ^2J = 11.3 Hz, ^3J = 6.2 Hz, 1H), 4.08 (dd, ^2J = 11.3 Hz, ^3J = 6.2 Hz, 1H), 3.96 (d, ^2J = 14.2 Hz, 1H), 3.70 (d, ^2J = 14.0 Hz, 1H), 3.29-3.22 (m, 1H), 2.96 (dd, ^2J = 13.1 Hz, ^3J = 6.1 Hz, 1H), 2.81 (dd, ^2J = 11.2 Hz, ^3J = 5.8 Hz, 1H), 2.04 (s, 6H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ = 170.7, 170.5, 138.3, 130.9, 128.6, 128.3, 127.2, 126.7, 65.0, 64.5, 58.3, 56.9, 49.9, 21.2, 21.0. **FT-IR** (neat, ATR): ν [cm^{-1}] = 2930 (w), 2850 (w), 1732 (s), 1452 (w), 1369 (m), 1222 (s), 1026 (m), 977 (w), 732 (w), 698 (m), 603 (w). **HRMS** (ESI): calcd for $C_{17}H_{21}NO_4$ *m*/*z* $[M+H]^+$: 304.1548, found: 304.1550.

(3*R*,6*R*)-6-(Hydroxymethyl)piperidin-3-ol 6



(3*R*,6*R*)-**6**

Diol **3b** (150 mg, 0.53 mmol) was dissolved in methanol (5 ml) and the resulting solution treated with $Pd(OH)_2$ (80 mg, 15-20 wt-% Pd on carbon). The round bottom flask was equipped with a hydrogen-filled balloon and stirred over night at room temperature. The reaction mixture was filtered through Celite and then evaporated under reduced pressure. **6** (69.0 mg, 0.53 mmol, 99% yield) was obtained as yellow oil. $[\alpha]^{20}_{D}$: +9.6 (c 0.77, $CHCl_3$). **^{1}H-NMR** (300 MHz, D_2O): δ [ppm] = 3.86-3.81 (m, 1H), 3.55 (d, 2H), 2.87 (ddd, ^2J = 13.5 Hz, ^3J = 3.1 Hz, ^3J = 2.1 Hz, 1H), 2.74 (dd, ^2J = 13.6 Hz, ^3J = 2.3 Hz, 1H), 2.69-2.61 (m, 1H), 1.76-1.57 (m, 2H), 1.44-1.36 (m, 2H). **^{13}C-NMR** (75 MHz, D_2O): δ = 64.4, 64.3, 55.6, 49.4, 28.9, 22.1. **FT-IR** (neat, ATR): ν [cm^{-1}] = 3284 (b), 2927 (w), 2858 (w), 2360 (s), 2341 (s), 1436 (w), 1056 (w), 1037 (w), 1001 (w), 958 (w), 935 (w), 675 (w). **HRMS** (ESI): calcd for $C_6H_{13}NO_2$ *m/z* $[M+H]^+$: 132.0980, found: 132.0990.

References

[1] Chong, H.; Garmestani, K.; Bryant Jr., L. H.; Brechbiel, M. W. *J. Org. Chem.* **2001**, *66*, 7745-7750.

[2] Sibi, M. P.; Lu, J. *Tetrahedron Lett*. **1994**, *35*, 4915-4918.

[3] Chen, Z.; Venkatesan , A. M.; Dos Santos, O.; Delos Santos, E.; Dehnhardt, C. M.; Ayral-Kaloustian, S.; Ashcroft, J.; McDonald, L. A.; Mansour, T. S. *J. Org. Chem*. **2010**, *75*, 1643-1651.