Supporting Information

Enantiopure 1,5-Diols from Dynamic Kinetic Asymmetric Transformation. Useful Synthetic Intermediates for the Preparation of Chiral Heterocycles

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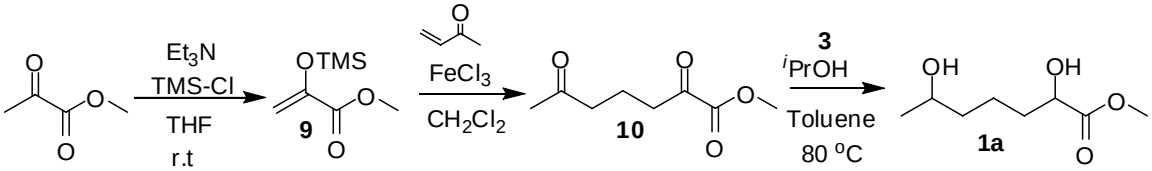
Experimental Section

General Procedures. All reactions were carried out under dry argon atmosphere in oven-dried or flame-dried glassware. ^{1}H NMR(400 or 300 MHz) and ^{13}C NMR (100 or 75 MHz) spectra were recorded on a Varian Mercury or a Bruker spectrometer with chemical shifts reported in ppm using the NMR solvent as a reference and coupling constants *J* in Hz. High resolution mass spectra (HRMS) were run on a Bruker MicroTOF (ESI-TOF) spectrometer. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. Isopropenyl acetate was distilled before use and sodium carbonate was dried using a bulb-to-bulb distillation equipment. All other commercially available reagents were used without further purification. Ruthenium catalysts **3**[i] and **4**[ii] as well as diol **1b**[iii], **1e**[iv] and **1g**[v] were synthesized according to literature procedures. Solvents for extraction and chromatography were of technical grade quality and distilled before use or purchased from Fischer in puriss quality. Purification of synthesized material was performed by flash chromatography using a Biotage SP1 system. The enantiomeric excess of compounds **1**, **2**, and **5** were determined by chiral GC employing a CP-Chirasil-Dex CB column using racemic diastereomeric mixtures as references.

Synthesis of 1,5-diols



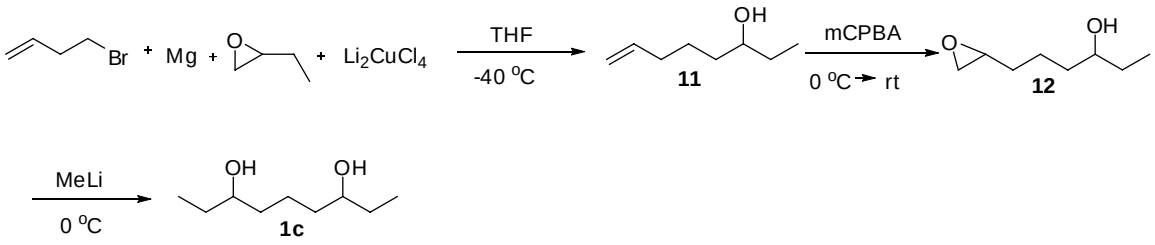
Scheme 1.

1-Carbomethoxy-1-(trimethylsiloxy)-ethylene (9). Et_3N (5.7 mL, 26 mmol) was added dropwise to a stirred solution of methyl pyruvate (2.6 mL, 34 mmol) and TMS-Cl (4.4 mL, 41 mmol) in 20 mL of dry CH_2Cl_2. The mixture was stirred at room temperature for 18 hours. Pentane was added and the white precipitate was filtered off. The organic phase was extracted with water and brine, dried with $MgSO_4$ and evaporated yielding **9** (4.05 g, 89%) as an oil. Analytical data agreed with those reported in the literature.[vi]

Methyl-2,6-dioxoheptanoate (10). $FeCl_3$ (374 mg, 2.3 mmol) was dissolved in 8 ml dry CH_2Cl_2 and cooled to 0 °C. Methyl vinyl ketone (5.6 mL, 69 mmol) was added, and then **9** (4 g, 23 mmol) was added dropwise. After the addition, the mixture was warmed to room

temperature and stirred for another 20 min. The solvent was evaporated and the residue was purified by chromatography (pentane: EtOAc 4:1 to EtOAc) afforded **10** (883 mg, 22%) as an oil. ^{1}H NMR ($CDCl_3$, 400MHz): δ 1.91 (2H, app. quint, *J*=7.0 Hz, CH_2), 2.13 (3H, s, CH_3), 2.51(2H, t, *J*=7.0 Hz, CH_2), 2.89 (2H, t, *J*=7.0 Hz, CH_2), 3.87 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.9, 29.9, 38.4, 42.0, 53.0, 161.3, 193.6, 207.9

Methyl-2,6-dihydroxyheptanoate (1a). Catalyst **3** (101 mg, 0.09 mmol) was dissolved in 6 mL of dry toluene and **10** (800 mg, 4.6 mmol) in 2-propanol (8 ml, 111 mmol) was added. After stirring at 70 °C for 16 hours the mixture was cooled to room temperature. Evaporation of the solvent and purification by chromatography (pentane:EtOAc 2:1 to EtOAc) afforded the title compound (573 mg, 70%) as a diastereomeric mixture. ^{1}H NMR ($CDCl_3$, 400MHz): δ 1.20 (3H, d, *J*=6.2, CH_3), 1.35 (1H, m, OH), 1.39-1.73 (5H, m, 3 x CH_2), 1.82 (1H, m, CH_2), 2.74 (1H, m, OH), 3.79 (3H, s, CH_3O), 3.81 (1H, m, CH), 4.20 (1H, m, CH), ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.0, 21.1, 23.5, 34.1, 38.7, 52.5, 67.8, 70.3 (both diastereomers), 175.6; HRMS (ESI) $(M + Li)^+$: m/z calcd for $C_8H_{16}LiO_4$ 183.1203, obsd 183.1200.



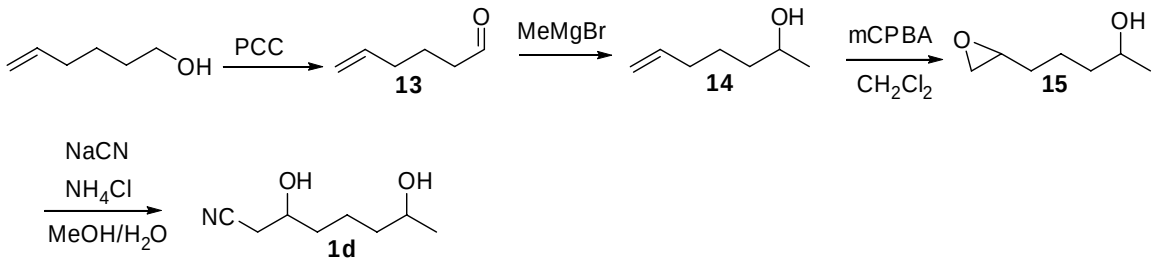
Scheme 2.

7-Octen-3-ol (11). [vii] To a two-necked round-bottomed flask fitted with a condenser and a dropping funnel was added Mg (384 mg, 15.8 mmol) and a crystal of I_2. 4-bromo-1-butene (1.52 mL, 15 mmol) and 25 mL dry THF was placed in the dropping funnel and some of the solution was added to the flask. The mixture was heated to reflux and the remaining solution was added dropwise under vigorous stirring. After complete addition, the mixture was stirred for another 30 min and then cooled to room temperature. 1,2-epoxybutane (0.86 mL, 10 mmol) was put in a 100 mL round-bottomed flask together with 17 mL of dry THF and the solution was cooled to -50 ºC. Li_2CuCl_4 (219 mg, 1 mmol) dissolved in 10 mL dry THF was added, followed by dropwise addition of the previously prepared Grignard reagent. The resulting dark blue mixture was stirred at -50 ºC for 1 h and then 5 mL of sat. NH_4Cl (aq) and 5 mL of water was added. The mixture was warmed to room temperature and extracted with

diethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated. Purification by chromatography (pentane: Et_2O 6:1 to Et_2O) afforded the title compound (1.04 g, 81%). ^1H NMR ($CDCl_3$, 400 MHz): δ 0.94 (3H, t, *J*=7.50 Hz, CH_3), 1.37-1.58 (6H, m, 3 x CH_2), 2.02-2.13 (2H, m, CH_2), 3.53 (1H, m, CH), 4.93-5.03 (2H, m, CH_2 =), 5.81 (1H, m, CH=). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 9.8, 24.9, 30.2, 33.7, 36.3, 73.2, 114.5, 138.7

7,8-Epoxyoctan-3-ol (12). 11 (1.04 g, 8.1 mmol) was dissolved in 130 mL of dry dichloromethane and cooled to 0 ºC. *m*-CPBA (50 wt%, 4.31 g, 12.1 mmol) was added in portions over 20 minutes, and the resulting mixture was left stirring at 0 ºC for 2h, and was then allowed to slowly warm to room temperature. After another 12 h, the mixture was cooled to 0 ºC and 70 mL of sat. Na_2SO_3 (aq) was added. The aqueous phase was extracted with dichloromethane and the combined organic phases were washed with sat. $NaHCO_3$ (aq) and brine, dried over $MgSO_4$ and concentrated. Purification by chromatography (CH_2Cl_2: Et_2O 9:1 to Et_2O) afforded epoxide **12** (820 mg; 70%) as a mixture of diastereomers. ^1H NMR ($CDCl_3$, 400 MHz): δ 0.94 (3H, t, *J*=7.5 Hz, CH_3), 1.38-1.63 (8H, m, 4 x CH_2), 2.48 (1H, dd, *J*=5.0, 2.8 Hz, CH_2 -O-), 2.75 (1H, app. t, *J*=5.0 Hz, CH_2 -O-), 2.92 (1H, m, CH -O-), 3.54 (1H, m, CH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 9.8 (both diasteromers), 22.0, 22.3, 30.2 (both diastereomers), 32.4 (both diasteromers), 36.5 (both diasteromers), 47.0, 47.1, 52.2, 52.3, 73.0, 73.1

Nonane-3,7-diol (1c). 12 (820 mg, 5.7 mmol) was dissolved in dry ether and cooled to 0 ºC. MeLi (1.6 M in Et_2O, 11 ml, 17 mmol) was added dropwise and the mixture was stirred at 0 ºC for 1 hour and then slowly warmed to room temperature. After stirring over night, the mixture was cooled to 0 ºC and water was added. The aqueous phase was extracted with ether and the combined organic phases were dried over $MgSO_4$ and concentrated. Purification by chromatography (Pentane: EtOAc 2:1 to EtOAc) afforded a diastereomeric mixture of diol **1c** (785 mg; 86%) as a solid. ^1H NMR ($CDCl_3$, 400 MHz): δ 0.93 (6H, t, *J*= 7.5 Hz, 2 x CH_3), 1.33-1.58 (10H, m, 5 x CH_2), 3.53 (2H, m, CH).^{13}C NMR ($CDCl_3$, 100 MHz): δ 9.9, 21.6, 21.8, 30.2 (both diastereomers), 36.6, 36.8, 73.2, 73.3 ; HRMS (ESI) $(M + Li)^+$: m/z calcd for $C_9H_{20}LiO_2$ 167.1618, obsd 167.1611.



Scheme 3.

5-Hexen-1-al (13). 5-Hexen-1-ol (4.8 mL, 40.3 mmol) was dissolved in 75 mL of dry CH_2Cl_2 and cooled to 0 ºC. PCC (13.05 g, 60.5 mmol) was added and the mixture was allowed to warm to room temperature. After stirring for 22 h, 75 mL pentane was added and the mixture was filtered through a silica plug. The plug was rinsed with 300 mL of a 1:1 mixture of CH_2Cl_2: pentane and the combined organic phases were evaporated yielding **13** (2.05 g; 52%) as an oil. Analytical data agreed with those reported in the literature[viii]

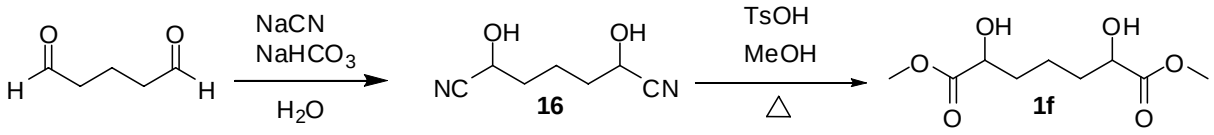
6-Hepten-2-ol (14). Aldehyde **13** (4.32 g, 27 mmol) was dissolved in dry ether (200 mL) and cooled to 0 ºC. MeMgBr (3 M in THF, 18 mL, 54 mmol) was added dropwise and the mixture was stirred at 0 ºC for 1 hour. NH_4Cl (aq) was added and the mixture was warmed to room temperature. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated, yielding **14** (2.3 g, 74%) as an oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.19 (3H, d, *J*= 6.3 Hz, CH_3), 1.38-1.57 (4H, m, 2 x CH_2), 2.05-2.10 (2H, m, CH_2), 3.81 (1H, m, CH), 4.93-5.03 (2H, m, CH_2 =), 5.80 (1H, m, CH =). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.5, 25.0, 33.6, 38.7, 68.0, 114.6, 138.7

6,7-Epoxyheptan-2-ol (15). 14 (1.6 g, 14 mmol) was dissolved in 230 mL dry dichloromethane and cooled to 0 ºC. *m*- CPBA (50 wt%, 7.45 g, 21 mmol) was added in portions over 20 minutes, and the resulting mixture was left stirring at 0 ºC for 30 minutes and was then allowed to slowly warm to room temperature. After another 22 h, the mixture was cooled to 0 ºC and 70 mL sat. Na_2SO_3 (aq) was added. The aqueous phase was extracted with dichloromethane and the combined organic phases were washed with sat. $NaHCO_3$ (aq) and brine, dried over $MgSO_4$ and concentrated. Purification by chromatography (DCM: Et_2O 6:1 to Et_2O) afforded epoxide **15** (1 g; 55%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.19 (3H, d, *J*=6.3 Hz, CH_3), 1.43-1.61 (6H, m, 3 x CH_2), 2.47 (1H, m, CH –O-), 2.74 (1H, m, CH –O-), 2.91 (1H, m, CH –O-), 3.80 (1H, m, CH). ^{13}C NMR

($CDCl_3$, 100 MHz): δ 22.1, 22.3, 23.5, 23.6, 32.3, 32.4, 38.8, 38.9, 47.0 (both diasteromers), 52.2, 52.3, 67.8, 67.9

3,7-Dihydroxy-octanenitrile (1d). [ix] To a solution of **15** (911 mg, 7 mmol) in a 8:1 mixture of MeOH:H_2O (65 mL) was added NaCN (1.71g, 35 mmol) and NH_4Cl (749 mg, 14 mmol) and the resulting mixture was heated to reflux for 26 h. After cooling to room temperature, MeOH was evaporated and the aqueous layer was saturated with NaCl (s) and extracted several times with EtOAc. The combined organic phases were dried over $MgSO_4$ and concentrated. Purification by chromatography (pentane: EtOAc 1:1 to EtOAc) afforded the title compound (787 mg; 72%) as a mixture of diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.20 (3H, d, *J*= 6.1 Hz, CH_3), 1.36-1.69 (6H, m, 3 x CH_2), 2.47-2.59 (2H, 2 x dd, *J*= 16.8, 6.3, 5.0, CH_2CN), 3.83 (1H, m, CH), 3.95 (1H, m, CH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.4 (both diastereomers), 23.5, 23.7, 26.1, 26.2, 36.0, 36.3, 38.1, 38.4, 67.2, 67.5, 67.7, 67.9, 117.9 (both diastereomers); HRMS (ESI) $(M + Li)^+$: m/z calcd for $C_8H_{15}LiNO_2$ 164.1257, obsd 164.1255.



2,6-dihydroxyheptadinitrile (16). Glutaric dialdehyde (4 mL, 25% solution in water, 10 mmol) was added to a solution of $NaHCO_3$ (5.38 g, 64 mmol) in 200 mL of water. Then sodium cyanide (3.2 g, 65 mmol) was added in portions and the resulting pale yellow mixture was stirred at room temperature for 12 h. NH_4Cl (aq) was added to pH 7, and the mixture was extracted with EtOAc. The combined organic layers were dried with $MgSO_4$ and concentrated. Purification by chromatography (pentane:EtOAc 1:1) afforded **16** (1.09 g, 70%) as a yellow oil. ^{1}H NMR (CD_3OD, 400MHz): δ 2.83 (2H, m, CH_2), 2.87-2.89 (4H, m, 2 x CH_2), 3.66 (2H, t, *J*=6.3 Hz, 2 × CH). ^{13}C NMR (CD_3OD, 100 MHz): δ 21.2, 35.8, 61.4, 121.7

2,6-Dihydroxy-heptanedioic acid dimethyl ester (1f). *p*-TsOH (5 g, 26 mmol) was added to a stirred solution of **15** (1.01 g, 6.6 mmol) in 4 ml MeOH. The resulting mixture was refluxed for 17 h and then cooled to room temperature. The solvent was evaporated and the residue was dissolved in water and extracted with EtOAc. The organic layers were dried ($MgSO_4$),

evaporated and purified by chromatography (pentane: EtOAc 1:2) to afford **1f** (577 mg, 40%) as a diasteromeric mixture. ^{1}H NMR ($CDCl_3$, 400MHz): δ 1.47-1.74 (4H, m, 2 x CH_2), 1.77-1.89 (2H, m, CH_2), 2.72 (2H, br s, 2 x OH), 3.79 (6H, s, 2 x CH_3O), 4.20 (2H, m, 2 x CH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.2, 20.4, 33.8 (both diastereomers), 52.5, 70.2 (both diastereomers), 175.5

Synthesis of (*R*)-6-Acetoxy-2-hydroxy-heptanoic acid methyl ester ((2*RS*,6*R*)-2a). CALB (45 mg), Na_2CO_3 (159 mg, 1.5 mmol) and ruthenium catalyst **4** (48 mg, 0.075 mmol) was put in a flame-dried Schlenk tube under argon. Then toluene (3.7 mL) and KO^{t}Bu (0.5 M in THF; 150 μL, 0.075 mmol) was added and after 6 min diol **1a** (258 mg, 1.5 mmol) was added. After another 4 min, acyl donor **6** (495 μL, 4.5 mmol) was added and the mixture was stirred at 80 ºC for 5 h and then filtered and concentrated. Purification by chromatography (pentane: EtOAc 3:1 to EtOAc) afforded (2*RS*,6*R*)-**2a** (178 mg, 56%) as a mixture of diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.20 (3H, d, *J*= 6.4 Hz, CH_3), 1.34-1.69 (5H, m, 3 x CH_2), 1.79 (1H, m, CH_2), 2.02 (3H, s, CH_3CO), 2.73 (1H, d, *J*= 5.5 Hz, OH), 3.78 (3H, s, CH_3O), 4.18 (1H, m, CH), 4.89 (1H, m, CH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.8, 19.9, 20.7 (both diastereomers), 21.3 (both diastereomers), 34.0 (both diastereomers), 35.4 (both diastereomers), 52.5, 70.2 (both diastereomers), 70.6, 70.7, 170.7, 175.6.

Dynamic Kinetic Asymmetric Transformation of 1,5-diols.

(2*S*,6*R*)-2,6-Diacetoxyheptanoic acid methylester ((2*S*,6*R*)-5a). Toluene (5 mL) was added to a flame-dried Schlenk tube containing enzyme (CALB) (60 mg), Na_2CO_3 (212 mg, 2.0 mmol) and ruthenium catalyst **4** (64 mg, 0.1 mmol) under argon. The Schlenk tube was evacuated and filled with argon and a solution of KO^{t}Bu (0.5 M in THF; 200 μL, 0.1 mmol) was added. The mixture was stirred for 6 min and diol **1a** (368 mg, 2.0 mmol) was then added, and after 4 min. isopropenyl acetate (**6**) (1320 μL, 12 mmol) was added. The mixture was stirred at 80 ^{o}C for a total of 72 h (after 5 h 20 mg of PS-C was added) and then filtered and concentrated. Purification by chromatography (pentane to 30 % EtOAc) afforded (2*S*,6*R*)-**5a** (368 mg, 71%) as an oil. The ee and diastereomeric ratio was determined by chiral GC; *ee* = 98%, *anti:syn* 80:20. $[\alpha]^{22}_{D}$ -13.4 (c 0.01, EtOAc), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.21 (3H, d, *J*= 6.3 Hz, CH_3), 1.35-1.66 (4H, m, 2 × CH_2), 1.80-1.87 (2H, m, CH_2), 2.03 (3H, s, CH_3), 2.14 (3H, s, CH_3), 3.74 (3H, s, CH_3O), 4.89 (1H, m, CH), 4.98 (1H, m, CH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.9, 20.6, 21.0, 21.3, 30.8, 35.3, 52.2, 70.4, 72.0, 170.5, 170.6, 170.7.

(*R*,*R*)-2,6-Diacetoxyheptane ((*R*,*R*)-5b). CALB (2.5 mg), Na_2CO_3 (106 mg, 1 mmol) and ruthenium catalyst **4** (16 mg, 0.025 mmol) was put in a flame-dried Schlenk tube under argon. Toluene (1 mL) was added followed by a solution of KO^{t}Bu (0.5 M in THF; 50 μL, 0.025 mmol). The mixture was stirred for 6 min and then diol **1b** (132 mg, 1 mmol) was added, and after another 4 min acyl donor **6** (330 μL, 3 mmol) was added. The mixture was stirred at 50 ºC for 24 h and then filtered and concentrated. Purification by chromatography (pentane: Et_2O 9:1 to Et_2O) afforded (*R*,*R*)-**5b** (172 mg, 80%) as an oil. The ee and diastereomeric ratio was determined by chiral GC; *ee* >99%, *anti:syn* 96:4. $[\alpha]^{22}_D$ -8.7 (c 0.004, EtOAc), NMR data agreed with those reported in the literature.[x]

(*R*,*R*)-3,7-Diacetoxynonane ((*R*,*R*)-5c). CALB (5 mg), Na_2CO_3 (106 mg, 1 mmol) and ruthenium catalyst **4** (32 mg, 0.05 mmol) was put in a flame-dried Schlenk tube under argon. Then toluene (2 mL) and KO^{t}Bu (0.5 M in THF; 100 μL, 0.05 mmol) was added and after 6 min diol **1c** (160 mg, 1 mmol) was added. After another 4 min, acyl donor **6** (330 μL, 3 mmol) was added and the mixture was left stirring at 50 ºC for 48 h. The mixture was filtered and concentrated and the residue was purified by chromatography (pentane: Et_2O 9:1 to Et_2O) yielding (*R*,*R*)-**5c** (180 mg, 73%) as an oil. The ee and diastereomeric ratio was determined by chiral GC; *ee* > 99%, *anti:syn* 94:6. $[\alpha]^{22}_D$ -6.9 (c 0.01, EtOAc), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.87 (6H, t, *J*= 7.5 Hz, 2 × CH_3), 1.28-1.34 (2H, m, CH_2), 1.45-1.60 (8H, m, 4 x CH_2), 2.04 (6H, s, 2 x CH_3CO), 4.78 (2H, m, 2 x CH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 9.6, 21.0, 21.2, 26.9, 33.4, 75.2, 170.9

(3*S*,7*R*)-3,7-Diacetoxyoctanenitrile ((3*S*,7*R*)-5d) CALB (100 mg), Na_2CO_3 (106 mg, 1 mmol) and ruthenium catalyst **4** (32 mg, 0.05 mmol) was put in a flame-dried Schlenk tube under argon. Then toluene (2.5 mL) and KO^{t}Bu (0.5 M in THF; 100 μL, 0.05 mmol) was added and after 6 min diol **1d** (157 mg, 1 mmol) was added. After another 4 min, acyl donor **6** (660 μL, 6 mmol) was added and the mixture was left stirring at 100 ºC for 40 h and then filtered and concentrated. Purification by chromatography (pentane: Et_2O 4:1 to Et_2O) afforded (3*S*,7*R*)-**5d** (147 mg, 61%) as an oil. The ee and diastereomeric ratio was determined by chiral GC; *ee* > 99%, *anti:syn* 94:6. $[\alpha]^{22}_D$ -24.0 (c 0.01, EtOAc), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.21 (3H, d, *J*= 6.3 Hz, CH_3), 1.33-1.41 (2H, m, CH_2), 1.46-1.71 (3H, m, 2 × CH_2), 1.82 (1H, m, CH_2), 2.03 (3H, s, CH_3CO), 2.10 (3H, s, CH_3CO), 2.57-2.74 (2H, dd, *J*= 5.5,

17.0 Hz, CH_2CN), 4.88 (1H, m, CH), 4.96 (1H, m, CH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.9, 20.9, 21.0, 21.3, 22.9, 33.0, 35.3, 68.5, 70.4, 116.2, 170.3, 170.7

(*R*,*R*)-*N*,*N*-bis-(2-acetoxypropyl)benzylamine ((*R*,*R*)-5e) CALB (2.5 mg), Na_2CO_3 (106 mg, 1 mmol) and ruthenium catalyst **4** (16 mg, 0.025 mmol) was put in a flame-dried Schlenk tube under argon. Toluene (1 mL) was added followed by a solution of KO^{t}Bu (0.5 M in THF; 50 μL, 0.025 mmol). The mixture was stirred for 6 min and then diol **1e** (223 mg, 1 mmol) was added, and after another 4 min acyl donor **6** (330 μL, 3 mmol) was added. The mixture was stirred at 50 ºC for 48 h and then filtered and concentrated. Purification by chromatography (pentane: Et_2O 6:1 to Et_2O) afforded the title compound (*R*,*R*)-**5e**(256 mg, 83%). The ee and diastereomeric ratio was determined by chiral GC; *ee* > 99%, *anti:syn* >99:1. $[\alpha]^{22}_D$ 33.3 (c 0.01, EtOAc), NMR data agreed with those reported in the literature. [x]

(*S*,*S*)-2,6-Diacetoxyheptanedioic acid dimethyl ester ((*S*,*S*)-5f). PS-C (10 mg), Na_2CO_3 (106 mg, 1 mmol) and ruthenium catalyst **4** (32 mg, 0.05 mmol) was put in a flame-dried Schlenk tube under argon. Toluene (2.5 mL) was added followed by a solution of KO^{t}Bu (0.5 M in THF; 120 μL, 0.06 mmol). The mixture was stirred for 6 min and then diol **1e** (194 mg, 0.9 mmol) was added, and after another 4 min acyl donor **6** (660 μL, 6 mmol) was added. The mixture was stirred at 80 ºC for 77 h and then filtered and concentrated. The conversion to diacetate was estimated to 77 % using chiral GC. The ee and diastereomeric ratio was determined by chiral GC; *ee* = 37 %, *anti:syn* 55:45. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.46-1.56 (2H, m, CH_2), 1.82-1.90 (4H, m, 2 × CH_2), 2.13 (6H, s, 2 × CH_3), 3.73 (6H, s, 2 × CH_3), 4.99 (2H, m, 2 × CH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.6, 20.9 (both diastereomers), 30.4, 30.5, 52.3, 71.8 (both diastereomers), 170.4 (2×C).

(*R*,*R*)-Bis-(2-acetoxypropyl) ether ((*R*,*R*)-5g). CALB (12.5 mg), Na_2CO_3 (530 mg, 5 mmol) and ruthenium catalyst **4** (80 mg, 0.125 mmol) was put in a flame-dried Schlenk tube under argon. Toluene (3 mL) was added followed by a solution of KO^{t}Bu (0.5 M in THF; 250 μL, 0.125 mmol). The mixture was stirred for 6 min and then diol **1g** (670 mg, 5 mmol) was added in 2 mL toluene, and after another 4 min acyl donor **6** (1652 μL, 15 mmol) was added. The mixture was stirred at 50 ºC for 46 h and then filtered and concentrated. Purification by chromatography (pentane: EtOAc 4:1 to EtOAc) afforded the title compound (*R*,*R*)-**5g** (884 mg, 81%). The ee and diastereomeric ratio was determined by chiral GC; *ee* > 99%, *anti:syn* 95:5. $[\alpha]^{22}_D$ -24.7 (c 0.01, EtOAc), ^1H NMR ($CDCl_3$, 400 MHz): δ 1.21 (6H, d, *J*= 6.4 Hz, 2 ×

CH_3), 2.04 (6H, s, 2 × CH_3), 3.44 (2H, dd, J= 4.3, 10.5 Hz, CH_2), 3.54 (2H, dd, J=6.1, 10.7 Hz, CH_2), 5.05 (2H, m, 2 × CH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.5, 21.3, 69.2, 73.5, 170.5

Synthesis of piperidines and morpholines

(*S,S*)-2,6-Dimethyl-1-(toluene-4-sulfonyl)-piperidine ((*S,S*)-7).

Prepared in three steps: 1) To a stirred solution of diacetate (*R,R*)-**5b** (216.3 mg, 1 mmol) in a 4:1 mixture of MeOH:H_2O (5 mL) was added NaOH (120 mg, 3 mmol). The mixture was refluxed for 1 h, then the mixture was allowed to cool to rt and the MeOH was evaporated and brine was added. The aqueous layer was extracted with EtOAc × 10. The combined organic phases were dried over $MgSO_4$ and evaporated, yielding (*R,R*)-**1b** (127.7 mg, 96 %) which was used without further purification.

2) The obtained diol (*R,R*)-**1b** (264 mg, 2 mmol) was dissolved in dry dichloromethane (10 mL) and cooled to 0 ºC. *i*- Pr_2NEt (3.48 mL, 20 mmol) was added followed by dropwise addition of MsCl (0.93 mL, 12 mmol). The resulting mixture was stirred at 0 ºC for 2 h and then at r.t for another 16 h. Water was added and the phases were separated. The aqueous phase was extracted with dichloromethane and the combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated. Purification by chromatography (pentane:EtOAc 2:1 to EtOAc) afforded the dimesylate (*R,R*)-**6b** (458 mg, 79 %).

3) The dimesylate (*R,R*)-**6b** (130 mg, 0.45 mmol) was dissolved in dry DMF (4 mL) and NaHNTs (260 mg, 1.35 mmol) and Cs_2CO_3 (147 mg, 0.45 mmol) was added. The resulting mixture was heated at 50 ºC for 48 h and was then allowed to cool to r.t. Water was added and the mixture was extracted with EtOAc. The organic phases were washed with water and brine, dried over $MgSO_4$ and evaporated. Purification by chromatography (pentane: Et_2O 7:1 to Et_2O) afforded piperidine (*S,S*)-**7** (83mg, 69 %). The ee and diastereomeric ratio was determined by chiral GC; *ee* > 99%, *anti:syn* 95:5. $[\alpha]^{22}_D$ 13.9 (c 0.01, EtOAc), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.24 (6H,d, *J*= 6.8 Hz, 2 × CH_3), 1.40-1.50 (2H, m, CH_2), 1.59-1.73 (4H, m, 2 × CH_2), 2.40 (3H, s, CH_3), 4.04 (2H, m, 2 × CH), 7.24 (2H, d, J= 8.5 Hz, Ar-H), 7.71 (2H, d, J= 8.3 Hz, Ar-H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.8, 19.1, 21.4, 32.5, 50.2, 126.8, 129.3, 141.7, 142.4

(*S,S*)-3,5-Dimethyl-4-(toluene-4-sulfonyl)-morpholine ((*S,S*)-8).

Prepared in three steps: 1) Diacetate (*R,R*)-**5g** (305mg, 1.4mmol) was dissolved in a 4:1 mixture of MeOH: H_2O (7.5 mL) and K_2CO_3 (580 mg, 4.2 mmol) was added. The resulting

mixture was stirred at rt for 4 days and then MeOH was evaporated. The aqueous phase was extracted with EtOAc × 15 and the combined organic layers were dried over $MgSO_4$ and evaporated, yielding (*R,R*)-**1g** (176 mg, 94 %) which was used without further purification.

2) The obtained diol (*R,R*)-**1g** (150 mg, 1.1 mmol) was dissolved in dry THF (12 mL) and cooled to 0 ºC. Et_3N (521 µL, 3.7 mmol) was added followed by dropwise addition of MsCl (289 µL, 3.7 mmol). The resulting mixture was stirred at 0 ºC for 1 h and then another 1.5 hours at r.t. Water was added and the phases were separated. The aqueous phase was extracted with ether. The combined organic layers were dried over $MgSO_4$ and evaporated. Purification by chromatography afforded dimesylate (*R,R*)-**6g** (255 mg, 80 %).

3) The dimesylate (*R,R*)-**6g** (203.1 mg, 0.7 mmol) was dissolved in dry DMF (7 mL) and NaHNTs (403.6 mg, 2.1 mmol) and Cs_2CO_3 (228 mg, 0.7 mmol) were added. The resulting mixture was heated at 50 ºC for 5 days and was then allowed to cool to r.t. Water was added and the mixture was extracted with EtOAc × 4. The organic phases were washed with water and brine, dried over $MgSO_4$ and evaporated. Purification by chromatography (pentane: EtOAc 4:1 to EtOAc) afforded morpholine (*S,S*)-**8** (153 mg, 81%). The ee and diastereomeric ratio was determined by chiral GC; *ee* > 99%, *anti:syn* 95:5. $[\alpha]^{22}_D$ 23.1 (c 0.006, EtOAc), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.21 (6H, d, *J*= 6.6 Hz, 2 × CH_3), 2.41 (3H, s, CH_3), 3.41 (2H, dd, J= 6.1, 11.4 Hz, CH_2), 3.70 (2H, dd,J= 3.1, 11.4 Hz, CH_2), 3.97 (2H, m, 2 × CH), 7.27 (2H, d, J= 7.9 Hz, Ar-H), 7.72 (2H, d,J= 8.3 Hz, Ar-H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 15.7, 21.5, 49.6, 72.6, 126.9, 129.5, 140.9, 143.0; HRMS (ESI) $(M + Na)^+$: m/z calcd for $C_{13}H_{19}NNaO_3S$ 292.0978, obsd 292.0965.

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