Dynamic Kinetic Resolution: an efficient route to *anti* a-amino-*ß*-hydroxy esters *via* Ru-SYNPHOS^{O} catalyzed hydrogenation

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Supporting Information:

Dichloromethane and dimethylformamide were distilled from calcium hydride and diethyl ether from sodium-benzophenone. Acetone for the catalyst preparation was distilled over potassium carbonate. Other solvents were used without any purification. Triethylamine was distilled from potassium hydroxide. All air and/or water sensitive reactions were carried out under an argon atmosphere unless otherwise noted.

^{1}H NMR spectra were recorded on an Avance 300 at 300 MHz or an Avance 400 at 400 MHz; ^{13}C NMR spectra were recorded on an Avance 300 at 75 MHz or an Avance 400 at 100 MHz. Chemical shifts (d) are reported in ppm downfield relative to internal Me_4Si. Coupling constants (*J*) are reported in Hz and refer to apparent peak multiplicities (recorded as s, singlet; d, doublet; t, triplet; q, quadruplet; qu, quintet; m, multiplet; and br, broad).

Mass spectra were determined on a Nermag R10-10C instrument. Ionization was obtained by chemical ionization with ammonia (DCI/NH_3) or by electrospray (on a API 3000 PE Sciex). Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 589 nm (sodium lamp). HPLC analyses of compounds **4** were conducted with Waters 600 system, using Daicel Chiralcel and Chiralpak chiral stationary phase columns.

The *ß*-keto ester **1d** is commercially available.

methyl 7-benzyloxy-3-oxo-heptanoate 1a[1].

To an ice-cooled suspension of KH (35% in mineral oil, previously washed with THF) (120 mmol, 1 eq., 13.70 g) in THF (20 mL) was added propan-1,3-diol (140 mmol, 1.16 eq., 10 mL) over 1 h. To this ice-cooled mixture was added carefully more propan-1,3-diol (970 mmol, 8 eq., 70 mL) followed by 1,3-dimethyl-3,4,5,6-tetrahydro-2(*1H*)-pyrimidone (12.40 mmol, 0.1 eq., 14 mL), *n*-Bu_4NI (10.80 mmol, 0.09 eq., 4.0 g) and benzyl bromide (120 mmol, 1.50 mL). The resulting slurry was then stirred at room temperature for 16 h before being quenched with saturated aqueous NH_4Cl (20 mL). After dilution with CH_2Cl_2, the mixture was washed with saturated aqueous NH_4Cl (250 mL). The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed successively with water and saturated aqueous NaCl, dried over Na_2SO_4 and concentrated under reduced pressure to give the crude alcohol. The residue was purified by silica gel column chromatography using cyclohexane:ethyl acetate (7:3) as eluent to give 3-benzyloxy propan-1-ol (17.27 g, 87% yield) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.35 (m, 5H), 4.53 (s, 2H), 3.76 (q, *J* = 4.8 Hz, 2H), 3.65 (t, *J* = 6.0 Hz, 2H), 2.88 (s, 1H), 1.87 (qu, *J* = 6.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.0, 128.2, 127.5, 73.0, 68.7, 61.0, 32.0. MS (DCI, NH_3): *m/z* 184 (100%, $[M+NH_4]^+$), 167 (28%, $[M+H]^+$).

To a solution of this alcohol (80 mmol, 13.30 g) in CH_2Cl_2 (85 mL) were added DMAP (3.6 mmol, 0.045 eq., 0.44 g), NEt_3 (94.6 mmol, 1.18 eq., 13.20 mL) and tosyl chloride (87.4 mmol, 1.1 eq., 16.66 g). The resulting mixture was stirred at room temperature for 5.5 h before being quenched first with saturated aqueous NH_4Cl (50 mL), then with water (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3*). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give the 3-benzyloxy-propyl 4-methylphenylsulfonate as a white paste-like solid, used without purification in the next step.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.32 (m, 5H), 7.25 (dd, *J* = 5.5, 7.5 Hz, 2H), 4.40 (s, 2H), 4.17 (t, *J* = 6.2 Hz, 2H), 3.50 (t, *J* = 6.0 Hz, 2H), 2.42 (s, 3H), 1.94 (qu, *J* = 6.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 144.6, 138.0, 132.9, 129.7, 128.2, 127.8, 127.5, 127.4, 72.9, 67.6, 65.5, 29.2, 21.5. MS (DCI, NH_3): *m/z* 338 (100%, $[M+NH_4]^+$), 321 (7%, $[M+H]^+$).

A solution of this sulfonate (80 mmol) and NaI (200 mmol, 2.5 eq., 30.0 g) in DMF (320 mL) was heated to 50°C for 4 h. An excess of NaI (40 mmol, 0.5 eq., 6.0 g) was added to the reaction mixture and heating was maintained for an additional hour. The reaction was cooled down to room temperature; CH_2Cl_2 (200 mL) and water (200 mL) were then added under vigorous stirring. After decantation, the organic layer was washed with water (3*200 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced

pressure. The residue was purified by silica gel column chromatography using cyclohexane:ethyl acetate (95:5) as eluent to give 3-benzyloxy iodopropane (18.85 g, 85% yield) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.38 (m, 5H), 4.57 (s, 2H), 3.59 (t, *J* = 5.9 Hz, 2H), 3.35 (t, *J* = 6.8 Hz, 2H), 2.14 (qu, *J* = 6.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.1, 128.3, 127.5, 73.0, 69.5, 33.4, 3.4. MS (DCI, NH_3): *m/z* 294 (100%, $[M+NH_4]^+$), 276 (7%, $[M]^+$).

To an ice-cooled suspension of NaH (60% in mineral oil, 36.9 mmol, 1.1 eq., 1.46 g) in THF (65 mL) was added dropwise a solution of methyl 3-oxo-butanoate (33.2 mmol, 3.57 mL) in THF (10 mL), the temperature of the reaction mixture being kept below 10°C. The resulting mixture was stirred for 20 min prior to the dropwise addition of *n*-BuLi (2.5M in hexane, 36.2 mmol, 1.09 eq., 14.50 mL), (temperature controlled below 10°C). After 10 min, a solution of 3-benzyloxy iodopropane (36.2 mmol, 1.09 eq., 10.0 g) in THF (10 mL) was added carefully. The reaction mixture was stirred for 6 h at room temperature before being quenched with a mixture of ice and HCl (2N). After 15 min of vigorous stirring and decantation, the aqueous layer was extracted with AcOEt. The combined organic layers were washed with saturated aqueous Na_2SO_3, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using cyclohexane:ethyl acetate (8:2) as eluent to give the *ß*-keto ester **1a** (5.21 g, 53% yield) as a yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.32 (m, 5H), 4.50 (s, 2H), 3.73 (s, 3H), 3.49 (t, *J* = 6.0 Hz, 2H), 3.44 (s, 2H), 2.57 (t, *J* = 6.9 Hz, 2H), 1.68 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 202.3, 167.5, 138.4, 128.2, 127.5, 127.4, 72.8, 69.8, 52.1, 48.9, 42.6, 28.8, 20.2. MS (DCI, NH_3): *m/z* 282 (100%, $[M+NH_4]^+$), 265 (39%, $[M+H]^+$).

methyl 3-oxo-octanoate 1b[2].

To an ice-cooled suspension of monomethyl malonate potassium salt (256.3 mmol, 2.3 eq., 40.0 g) in THF (300 mL) was added NEt_3 (245 mmol, 2.2 eq., 34.1 mL) followed by $MgCl_2$ (312 mmol, 2.8 eq., 29.71 g). The resulting mixture was then stirred at room temperature for 3.5 h before being cooled again to 0°C. To this reaction mixture were added hexanoyl chloride (111.43 mmol, 15.8 mL) and NEt_3 (25.6 mmol, 0.23 eq., 3.6 mL) and the stiring was maintained at room temperature for 18 h. The solvent was removed under reduced pressure and the resulting mixture was then diluted with Et_2O (800 mL) and 10% HCl was added until disparition of the precipitate. The aqueous layer was decanted and the organic layer washed successively with saturated aqueous $NaHCO_3$, water and saturated aqueous NaCl, dried over $MgSO_4$ and concentrated under reduced pressure to give the crude *ß*-keto ester as a slightly brown oil. The residue was purified by silica gel column chromatography using cyclohexane:ethyl acetate (95:5 -> 90:10) as eluent to give **1b** (17.45 g, 91% yield) as a clear brown liquid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.71 (s, 3H), 3.43 (s, 2H), 2.51 (t, *J* = 7.5 Hz, 2H), 1.57 (qu, *J* = 7.5 Hz, 2H), 1.27 (m, 4H), 0.86 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ202.8, 167.7, 52.2, 49.0, 43.0, 31.1, 23.1, 22.3, 13.8. MS (DCI, NH_3): *m/z* 190 (100%, $[M+NH_4]^+$), 173 (6%, $[M+H]^+$).

methyl 3-oxo-octadecanoate 1c[3].

To a suspension of palmitic acid (60 mmol, 15.4 g) in THF (140 mL) was added in small portions *N*,*N'*-carbonyldiimidazole (72 mmol, 1.2 eq., 11.7 g). After evolution of gas, the reaction mixture was stirred at room temperature for 6 h. The bis-(mono-methyl malonate) magnesium salt (72 mmol, 1.2 eq., 18.6 g) was poured progressively into this solution under vigorous stirring. After being stirred at room temperature for 36 h, the mixture was concentrated under reduced pressure. Et_2O was added to the residue and the resulting mixture was acidified to pH 4 with 10% HCl and extracted with Et_2O (2*200 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (200 mL), dried over $MgSO_4$ and condensed under reduced pressure to give the crude *ß*-keto ester, which was purified by silica gel column chromatography using cyclohexane:ethyl acetate (9:1) as eluent to give **1c** (11.3 g, 60% yield) as a white powder.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.73 (s, 3H), 3.44 (s, 2H), 2.52 (t, *J* = 7.4 Hz, 2H), 1.57 (m, 2H), 1.24 (br s, 24H), 0.87 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ202.8, 167.7, 52.3, 49.0, 43.1, 31.9, 29.5, 29.3, 29.0, 23.4, 22.7, 14.1. MS (DCI, NH_3): *m/z* 330 (100%, $[M+NH_4]^+$), 313 (5%, $[M+H]^+$).

General Procedure for the synthesis of the a-hydroxyimino-*ß*-keto esters 2.

*With sodium nitrite (**2a**, **2d**):

A solution of the *ß*-keto ester **1** (31 mmol) in acetic acid (20 mL) was cooled to 0°C and a suspension of $NaNO_2$ (77.5 mmol, 2.5 eq., 5.35 g) in water (17 mL) was added dropwise, the temperature of the reaction mixture being kept below 5°C. After evolution of the brown fumes, the stirring was maintained 2 h at 0°C and

then at room temperature until completion of the reaction, monitored by TLC. The reaction mixture was then diluted and extracted with Et_2O (3*50 mL); the combined organic layers were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated under reduced pressure to give the a-hydroxyimino-*ß*-keto ester **2**.

methyl 7-benzyloxy-2-hydroxyimino-3-oxo-heptanoate 2a.

Obtained from **1a** in 84% yield as a white solid after purification by silica gel column chromatography (cyclohexane:ethyl acetate 7:3).

m.p. 52°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.65 (s, 1H), 7.34 (m, 5H), 4.54 (s, 2H), 3.91 (s, 3H), 3.52 (t, *J* = 6.0 Hz, 2H), 2.83 (t, *J* = 6.9 Hz, 2H), 1.72 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 195.6, 162.2, 150.4, 137.4, 128.4, 127.9, 73.0, 70.0, 52.6, 37.4, 29.0, 20.3. MS (DCI, NH_3): *m/z* 311 (100%, $[M+NH_4]^+$), 294 (3%, $[M+H]^+$).

ethyl 2-hydroxyimino-4-methyl-3-oxo-pentanoate 2d.

Obtained from **1d** in 90% yield as a white syrup, which partially solidified and used without purification in the next step.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.30 (q, *J* = 7.2 Hz, 2H), 3.32 (heptuplet, *J* = 6.9 Hz, 1H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.16 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ201.1, 162.0, 149.7, 62.4, 35.5, 18.3, 13.9. MS (DCI, NH_3): *m/z* 205 (100%, $[M+NH_4]^+$).

*With *n*-butyl nitrite (**2b**, **2c**):

To a solution of *ß*-keto ester **1** (10 mmol) in Et_2O (40 mL) was added *n*-$BuNO_2$ (20 mmol, 2 eq., 2.3 mL). The resulting mixture was cooled to 0°C prior to the dropwise addition of a 4N etheral solution of HCl (40 mmol, 4 eq., 10 mL). The stirring was maintained 1 h at 0°C and then at room temperature until completion of the reaction, monitored by TLC. Cold water (125 mL) was then poured into the reaction mixture. The aqueous layer was decanted and extracted twice with Et_2O and the combined organic layers were dried over $MgSO_4$ and condensed under reduced pressure to give the a-hydroxyimino-*ß*-keto ester **2**.

methyl 2-hydroxyimino-3-oxo-octanoate 2b.

Obtained from **1b** in 91% yield as a yellow oil after purification by silica gel column chromatography (cyclohexane:ethyl acetate 8:2).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.17 (s, 1H), 3.89 (s, 3H), 2.78 (t, *J* = 7.4 Hz, 2H), 1.63 (qu, *J* = 7.4 Hz, 2H), 1.29 (m, 4H), 0.88 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ196.6, 162.2, 150.4, 52.6, 37.4, 31.0, 23.2, 22.1, 13.5. MS (DCI, NH_3): *m/z* 219 (100%, $[M+NH_4]^+$), 202 (2%, $[M+H]^+$).

methyl 2-hydroxyimino-3-oxo-octadecanoate 2c[3].

Obtained from **1c** in quantitative yield as a white powder and used without purification in the next step.

m.p. 49°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.0 (br s, 1H), 3.90 (s, 3H), 2.78 (t, *J* = 7.4 Hz, 2H), 1.62 (m, 2H), 1.26 (br s, 24H), 0.87 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ196.1, 162.0, 150.6, 52.8, 37.8, 31.9, 29.5, 29.1, 23.7, 23.6, 14.1. MS (DCI, NH_3): *m/z* 359 (100%, $[M+NH_4]^+$).

General Procedure for the synthesis of the a-amino-*ß*-keto ester hydrochlorides 3 (except 3a).

To a solution of 2-hydroxyimino-*ß*-keto ester **2** (5 mmol) in alcohol (R'OH = MeOH or EtOH) (15 mL) was added Pd/C 10% (1.67 mmol, 0.33 eq., 178 mg). 3N alcoholic (R'OH) HCl (15 mmol, 3.3 eq., 5 mL) was added dropwise to the resulting mixture and the argon atmosphere was replaced with hydrogen. The reaction mixture was stirred at room temperature under atmospheric pressure of hydrogen for 24 h (reaction monitored by TLC). The suspension was then filtered on a celite pad and washed with R'OH. The filtrate was concentrated under reduced pressure to give the *ß*-keto ester hydrochloride **3**.

methyl 2-amino-3-oxo-octanoate hydrochloride 3b.

Obtained from **2b** in quantitative yield as a white powder and used without purification in the next step.

m.p. 76°C. ^{1}H NMR (MeOD, 300 MHz): δ 3.93 (s, 3H), 2.86 (qt, *J* = 7.1, 19.4 Hz, 2H), 1.65 (qu, *J* = 7.1 Hz, 2H), 1.34 (m, 4H), 0.93 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (MeOD, 75 MHz): δ199.5, 165.3, 62.3, 54.6, 41.4, 32.1, 23.9, 23.4, 14.2. ESI-MS: *m/z* 210 $[M\text{-}HCl+Na]^+$, 188 $[M\text{-}HCl+H]^+$. HRMS (DCI^+): *m/z* calcd. for $C_9H_{18}O_3N$: 188.1287, found: 188.1289.

methyl 2-amino-3-oxo-octadecanoate hydrochloride 3c.

Obtained from **2c** in quantitative yield as a slightly yellow powder and used without purification in the next step.

dec. 200°C. ^{1}H NMR (MeOD, 400 MHz): δ 3.87 (s, *3*H), 2.85 (dt, *J* = 7.2 Hz, 1H), 2.74 (dt, *J* = 6.8 Hz, 1H), 1,59 (m, 2H), 1.25 (s, 24H), 0.85 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (MeOD, 100 MHz): δ198.1, 163.9, 117.6, 53.2, 40.0, 31.7, 29.4, 29.2, 29.1, 28.6, 22.9, 22.3, 13.1. ESI-MS: *m/z* 350.3 $[M\text{-}HCl+Na]^+$, 328.6 $[M\text{-}HCl+H]^+$. HRMS (DCI^+): *m/z* calcd. for $C_{19}H_{38}O_3N$: 328.2852, found: 328.2862.

ethyl 2-amino-4-methyl-3-oxo-pentanoate hydrochloride 3d.

Obtained from **2d** in quantitative yield as a slightly green powder and used without purification in the next step.

m.p. 115°C. ^{1}H NMR (MeOD, 300 MHz): δ 4.37 (q, *J* = 7.1 Hz, 2H), 3.25 (q, *J* = 6.8 Hz, 1H), 1,35 (t, *J* = 7.1 Hz, 3H), 1.23 (d, *J* = 7.1 Hz, 3H), 1.12 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (MeOD, 100 MHz): δ203.8, 164.7, 64.8, 39.8, 19.1, 17.7, 14.2. ESI-MS: *m/z* 369.3 $[2(M\text{-}HCl)+Na]^+$, 347.3 $[2(M\text{-}HCl)+H]^+$, 196.0 $[M\text{-}HCl+Na]^+$, 173.9 $[M\text{-}HCl+H]^+$. HRMS (DCI^+): *m/z* calcd. for $C_8H_{16}O_3N$: 174.1130, found: 174.1134.

methyl 2-amino-7-benzyloxy-3-oxo-heptanoate hydrochloride 3a.

To an ice-cooled solution of 2-hydroxyimino-*ß*-keto ester **2a** (7.5 mmol, 2.20 g) in acetic acid (35 mL) was added Boc_2O (87 mmol, 11.6 eq., 20 mL) followed by zinc dust (75 mmol, 10 eq., 4.26 g) in small portions. The reaction mixture was then heated 1 h at 50°C. After cooling down, water (85 mL) was added and the resulting mixture was filtered on a celite pad and the zinc cake was washed with CH_2Cl_2. The aqueous layer was decanted and extracted twice with Et_2O. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using cyclohexane:ethyl acetate (95:5 -> 80:20) as eluent to give the desired product (2.49 g, 87% yield) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.30 (m, 5H), 5.73 (d, *J* = 7.1 Hz, 1H), 5.02 (d, *J* = 7.1 Hz, 1H), 4.47 (s, 2H), 3.76 (s, 3H), 3.45 (t, *J* = 6.0 Hz, 2H), 2.65 (m, 2H), 1.64 (m, 4H), 1.43 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz):δ 201.1, 167.1, 154.8, 138.4, 128.3, 127.6, 127.5, 80.5, 72.8, 69.7, 63.4, 53.0, 40.2, 28.8, 28.2, 20.2. MS (DCI, NH_3): *m/z* 397 (100%, $[M+NH_4]^+$), 380 (13%, $[M+H]^+$), 341 (35%, $[M\text{-}C_4H_8+NH_4]^+$).

A solution of this a-NHBoc-*ß*-keto ester (4 mmol, 1.50 g) in 3N methanolic HCl (20 mmol, 5eq., 6.70 mL) was stirred at room temperature for 16 h. 3N methanolic HCl (20 mmol, 5eq., 6.70 mL) was added once more and the stirring was maintained for 6 additional hours. The solvent was then removed under reduced pressure. The chlorhydrate **3a** was obtained as a white powder (1.19 g, 94% yield), used without purification in the next step.

m.p. 88°C. ^{1}H NMR (MeOD, 300 MHz): δ 7.30 (m, 5H), 4.49 (s, 2H), 3.89 (s, 3H), 3.51 (t, *J* = 6.0 Hz, 2H), 2.88 (m, 2H), 1.68 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 199.4, 165.2, 139.8, 129.4, 128.9, 128.7, 73.9, 710, 54.6, 41.1, 29.8, 21.2. ESI-MS: *m/z* 302.5 $[M\text{-}HCl+Na]^+$, 280.2 $[M\text{-}HCl+H]^+$. HRMS (DCI^+): *m/z* calcd. for $C_{15}H_{22}O_4N$: 280.1549, found: 280.1552.

General Procedure for the preparation of the catalyst [Ru(diphosphine)Br_2].

(*S*)-SYNPHOS® (0.011 mmol, 1.1 eq., 7.1 mg) and Ru(cyclooctadiene)[η^3-$(CH_2)_2CHCH_3]_2$ (0.01 mmol, 3.2 mg) were placed in a 15 mL Schlenk tube and the vessel was purged with argon. Anhydrous acetone (1 mL) previously degassed by three vacuum-argon cycles was added at room temperature. To this suspension was added dropwise methanolic HBr (0.022 mmol, 2.2 eq., 141 µL of a 0.156N solution prepared by added 48% aqueous HBr in degassed methanol) and the suspension was stirred at room temperature for 30 min. The suspension immediately turned yellow, then an orange precipitated appeared and the solvent was thoroughly evaporated under vacuum to give the catalyst as an orange-brown solid, which was used directly.

General Procedure for the synthesis of the *anti* a-amino-*β*-hydroxy ester (2*S*,3*S*)-4 and (2*R*,3*R*)-4.

To the catalyst [Ru(*S*)-SYNPHOS®Br_2] (0.01 mmol, 2 mol%, freshly prepared according to the general procedure), the a-amino-*β*-keto ester hydrochloride **3** (0.5 mmol) was added followed by previously degassed anhydrous CH_2Cl_2 (2 mL) and degassed alcoholic solvent R'OH (MeOH or EtOH) (200 µL). The Schlenk vessel was degassed by three vacuum-argon cycles and then placed under argon in a 250 mL stainless steel autoclave. The argon atmosphere was replaced with hydrogen by three cycles of pressurizing and the pressure adjusted to 12 bar. The autoclave was heated at 50°C and stirring was maintained for 24 hours. After cooling, the reaction mixture was concentrated under reduced pressure to afford the crude *β*-hydroxy ester. ^{1}H NMR (MeOD) analysis showed a complete conversion.

To an ice-cooled solution of the crude a-amino-*β*-hydroxy ester hydrochloride (0.5 mmol) in anhydrous CH_2Cl_2 (5 mL) was added benzoic anhydride (0.55 mmol, 1.1 eq., 122 mg) followed by NEt_3 (0.6 mmol, 1.2 eq., 84 µL). After 15 min at 0°C, the stirring was maintained 20 h at room temperature. The mixture was then concentrated under reduced pressure. THF (10 mL) was added to the residue and the mixture was stirred for 15 min. The resulting precipitate was removed by filtration on a celite pad and washed with THF. The filtrate was concentrated under reduced pressure.

methyl (2*S*,3*S*)-2-benzoylamino-7-benzyloxy-3-hydroxy-heptanoate (2*S*,3*S*)-4a.

Obtained from **3a** as a brown solid in 94% yield over two steps (hydrogenation with the catalyst [Ru(*S*)-SYNPHOS®Br_2] and reprotection), after purification by silica gel column chromatography (cyclohexane:ethyl acetate 6:4).

m.p. 42°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.82 (d, *J* = 7.0 Hz, 2H), 7.51 (t, *J* = 7.2 Hz, 1H), 7.42 (t, *J* = 7.0 Hz, 2H), 7.28 (m, 5H), 4.87 (dd, *J* = 3.2, 7.3 Hz, 1H), 4.48 (s, 2H), 4.04 (m, 1H), 3.77 (s, 3H), 3.46 (t, *J* = 6.1 Hz, 2H), 1.57 (m, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.9, 167.8, 138.4, 133.3, 131.9, 128.6, 128.3, 127.6, 127.5, 127.2, 73.0, 72.8, 70.1, 58.0, 52.6, 33.1, 29.4, 22.5. MS (DCI, NH_3): *m/z* 386 (100%, $[M+H]^+$). $[\alpha]^{21}_D$ = + 26 (*c* = 1.0, $CHCl_3$). HPLC Chiralcel OD-H, 95:5 hexane:*iso*-propanol, 1 mL/min, λ=254 nm, t_R 75.68 min.

methyl (2*R*,3*R*)-2-benzoylamino-7-benzyloxy-3-hydroxy-heptanoate (2*R*,3*R*)-4a.

Obtained from **3a** as a brown solid in 93% yield over two steps (hydrogenation with the catalyst [Ru(*R*)-SYNPHOS®Br_2] and reprotection), after purification by silica gel column chromatography (cyclohexane:ethyl acetate 6:4).

Physical data identical to **(2*S*,3*S*)-4a**. $[\alpha]^{21}_D$ = - 28 (*c* = 1.0, $CHCl_3$). HPLC Chiralcel OD-H, 95:5 hexane:*iso*-propanol, 1 mL/min, λ=254 nm, t_R 50.89 min.

methyl (2*S*,3*S*)-2-benzoylamino-3-hydroxy-octanoate (2*S*,3*S*)-4b.

Obtained from **3b** as a yellow oil in 85% yield over two steps (hydrogenation with the catalyst [Ru(*S*)-SYNPHOS®Br_2] and reprotection), after purification by silica gel column chromatography (cyclohexane:ethyl acetate 7:3).

m.p. 60°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.82 (d, *J* = 6.4 Hz, 2H), 7.46 (m, 3H), 7.24 (br d, *J* = 8.0 Hz, 1H), 4.88 (dd, *J* = 3.2, 7.3 Hz, 1H), 4.04 (m, 1H), 3.80 (s, 3H), 1.49 (m, 4H), 1.28 (m, 4H), 0.87 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ171.0, 167.9, 133.3, 131.9, 128.6, 127.2, 73.2, 58.0, 52.7, 33.4, 31.5, 25.3, 22.5, 14.0. MS (DCI, NH_3): *m/z* 294 (100%, $[M+H]^+$). HRMS (DCI^+): *m/z* calcd. for $C_{16}H_{24}O_4N$: 294.1705, found: 294.1711. $[\alpha]^{21}_D$ = + 26 (*c* = 1.0, $CHCl_3$). HPLC: Chiralpak AS-H, 98:2 hexane:*iso*-propanol, 1.0 mL/min, λ=254 nm, t_R 66.29 min.

methyl (2*R*,3*R*)-2-benzoylamino-3-hydroxy-octanoate (2*R*,3*R*)-4b.

Obtained from **3b** as a yellow oil in 90% yield over two steps (hydrogenation with the catalyst [Ru(*R*)-SYNPHOS®Br_2] and reprotection), after purification by silica gel column chromatography (cyclohexane:ethyl acetate 7:3).

Physical data identical to **(2*S*,3*S*)-4b**. $[\alpha]^{21}_D$ = - 27 (*c* = 1.0, $CHCl_3$). HPLC: Chiralpak AS-H, 98:2 hexane:*iso*-propanol, 1.0 mL/min, λ=254 nm, t_R 50.83 min.

methyl (2*S*,3*S*)-2-benzoylamino-3-hydroxy-octadecanoate (2*S*,3*S*)-4c.

Obtained from **3c** as a brown solid in 83% yield over two steps (hydrogenation with the catalyst [Ru(*S*)-SYNPHOS®Br_2] and reprotection), after purification by silica gel column chromatography (cyclohexane:ethyl acetate 8:2).

m.p. 87°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.84 (m, 2H), 7.50 (m, 3H), 7.15 (br d, *J* = 6.9 Hz, 1H), 4.89 (dd, *J* = 3.1, 6.9 Hz, 1H), 4.05 (m, 1H), 3.83 (s, 3H), 1.50 (m, 2H), 1.25 (br s, 26H), 0.88 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ171.0, 167.9, 132.1, 130.1, 128.7, 127.2, 73.3, 58.1, 52.7, 33.4, 31.9, 29.7, 25.7, 22.7, 14.1. MS (DCI, NH_3): *m/z* 434 (100%, $[M+H]^+$). HRMS (DCI^+): *m/z* calcd. for $C_{26}H_{44}O_4N$: 434.3270, found: 434.3264. $[\alpha]^{21}_D$ = + 19 (*c* = 0.8, $CHCl_3$). HPLC: Chiralpak AS-H, 98:02 hexane:*iso*-propanol, 1.0 mL/min, λ=254 nm, t_R 32.31 min.

methyl (2*R*,3*R*)-2-benzoylamino-3-hydroxy-octadecanoate (2*R*,3*R*)-4c.

Obtained from **3c** as a brown solid in 85% yield over two steps (hydrogenation with the catalyst [Ru(*R*)-SYNPHOS®Br_2] and reprotection), after purification by silica gel column chromatography (cyclohexane:ethyl acetate 8:2).

Physical data identical to **(2*S*,3*S*)-4c**. $[\alpha]^{21}_D$ = - 22 (*c* = 0.8, $CHCl_3$); HPLC: Chiralpak AS-H, 98:02 hexane:*iso*-propanol, 1.0 mL/min, λ=254 nm, t_R 26.37 min.

ethyl (2*S*,3*S*)-2-benzoylamino-3-hydroxy-4-methyl-pentanoate (2*S*,3*S*)-4d.

Obtained from **3d** as a slightly brown powder in 90% yield over two steps (hydrogenation with the catalyst [Ru(*S*)-SYNPHOS®Br_2] and reprotection), after purification by silica gel column chromatography (cyclohexane:ethyl acetate 8:2).

m.p. 86°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.82 (m, 2H), 7.47 (m, 3H), 7.20 (br d, *J* = 6.9 Hz, 1H), 4.93 (dd, *J* = 3.1, 7.2 Hz, 1H), 4.28 (dq, *J* = 1.9, 7.2 Hz, 2H), 3.63 (dd, *J* = 3.2, 8.7 Hz, 1H), 1.79 (m, 1H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.06 (d, *J* = 6.6 Hz, 3H), 1.03 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ171.0, 167.5, 133.5, 131.9, 128.6, 127.1, 78.9, 61.9, 56.2, 31.6, 19.0, 14.1. MS (DCI, NH_3): *m/z* 280 (100%, $[M+H]^+$). HRMS (DCI^+): *m/z* calcd. for $C_{15}H_{22}O_4N$: 280.1549, found: 280.1551. $[\alpha]^{21}_D$ = + 33 (*c* = 1.0, $CHCl_3$). HPLC: Chiralcel OJ, 96:04 hexane:*iso*-propanol, 1.0 mL/min, λ=254 nm, t_R 19.31 min.

ethyl (2*R*,3*R*)-2-benzoylamino-3-hydroxy-4-methyl-pentanoate (2*R*,3*R*)-4d.

Obtained from **3d** as a slightly brown powder in 96% yield over two steps (hydrogenation with the catalyst [Ru(*R*)-SYNPHOS®Br_2] and reprotection), after purification by silica gel column chromatography (cyclohexane:ethyl acetate 8:2).

Physical data identical to **(2*S*,3*S*)-4d**. $[\alpha]^{21}_D$ = - 38 (*c* = 1.0, $CHCl_3$); HPLC: Chiralcel OJ, 96:04 hexane:*iso*-propanol, 1.0 mL/min, λ=254 nm, t_R 15.82 min.

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