General procedure for alkylation of β-hydroxy esters.

LDA (2.1 eq.) was generated by the addition of nBuLi (2.55M in THF) to a solution of diisopropylamine (2.1 eq.; 1.0 M in THF) at 0 °C. After 15 minutes, the LDA solution was cooled to –78 °C and a THF solution of β-hydroxy ester **4a-g** (1.0 eq.) was added dropwise via syringe such that the internal temperature was maintained at or below –65 °C. The alkylating agent (1.1 eq.) was added via syringe followed by DMPU (10% v/v). The reaction mixture was stirred at –78 °C for 5 minutes then allowed to come to 0 °C over 24-48h until reaction was complete by TLC. Reaction mixtures were quenched with saturated NH_4Cl and extracted into ether then washed with 1 N HCl, 5% $NaHCO_3$ and brine and dried over $MgSO_4$. Crude aldol products **5a-i**, **5s-t** were purified by silica gel chromatography (Hexanes:EtOAc).

Compounds **5a, 5e, 5f, 5h,** and **5i** were hydrogenated in methanol over 10% Pd/C or palladium hydroxide at 1-3 atm. and the reaction was monitored by NMR until hydrogenation was complete. The reaction mixture was filtered through Celite and concentrated to afford the saturated hydroxy esters **5j, 5n, 5o, 5q,** and **5r**, respectively.

Compounds **5b, 5c, 5d,** and **5g** were hydrogenated in methanol over Rh/Al_2O_3 at 70 psi for 24-48 h. Crude reaction mixtures were filtered through Celite and concentrated to provide cyclohexyl derivatives **5k, 5l, 5m,** and **5p**, respectively.

Methyl (2*R*,3*R*)-2-(2-Methyl-2-propen-1-yl)-3-hydroxyhexanoate (5a).

Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.82 (s, 1H), 4.75 (s, 1H), 3.70 (s, 3H), 3.68 (m, 1H), 2.70 (m, 1H), 2.50 (m, 1H), 2.35 (dd, 1H), 1.75 (s, 3H), 1.60-1.65 (m, 4H), 0.95 (t, 3H) ppm.

Methyl (2*R*,3*R*)-2-benzyl-3-cyclopropyl-3-hydroxypropanoate (5b).

Oil (40%). 5:1 ratio of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3-7.4 (m, 2H), 7.2-7.3 (m, 3H), 3.65 (s, 3H), 3.61 (s, minor syn diastereomer), 3.1-3.2 (m, 2H), 2.9-3.0 (m, 2H), 2.56 (d, 1H, *J*=6 Hz, OH), 0.9-1.0 (m, 1H), 0.5-0.7 (m, 2H), 0.3-0.4 (m, 1H), 0.2-0.3 (m, 1H). ESI-MS m/z 257 $(M+Na)^+$.

Methyl (2*R*,3*R*)-3-hydroxy-4-methyl-2-(4-methylbenzyl)pentanoate (5c). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.1 (m, 4H), 3.65 (s, 3H), 3.65 (s, 3H), 3.3 (m, 1H), 3.0

(m, 3H), 2.7 (d, 1H), 2.3 (s, 3H), 1.7 (m, 1H), 1.0 (d, 3H), 0.95 (d, 3H) ppm; ESI-MS m/z 273 $(M+Na)^+$.

Methyl (3*R*)-6,6,6-trifluoro-3-hydroxy-2-phenylmethylhexanoate (5d). Oil (65%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.20 (m, 5H), 3.51 (s, 3H), 3.48 (m, 1H), 3.05 (m, 2H), 2.73 (m, 1H), 2.46-2.35 (m, 1H), 2.20-2.05 (m, 1H), 1.76-1.60 (m, 2H).

Methyl (2*R*,3*R*)-2-(2-Methyl-2-propen-1-yl)-3-hydroxybutanoate (5e). Oil (28%). ^1H NMR (400 MHz, $CDCl_3$) δ 4.80 (s, 1H), 4.77 (s, 1H), 3.90 (m, 1H), 3.69 (s, 3H), 2.68 (m, 1H), 2.52-2.41 (m, 2H), 2.36 (m, 1H), 1.5 (s, 3H), 1.22 (d, J = 6.8 Hz, 3H) ppm. APCI-MS m/z 173 $(M+H)^+$.

Methyl (2*S*)-2-[(1*R*)-1-hydroxy-2-phenylethyl]-4-methylpent-4-enoate (5f). Oil (75%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.29-7.31 (m, 2H), 7.20-7.25 (m, 3H), 4.77 (bs, 1H), 4.73 (bs, 1H), 3.85-3.95 (m, 1H), 3.71 (s, 3H), 2.75-2.88 (m, 2H), 2.70-2.78 (m, 1H), 2.42 (ABX, 2H, *J*=11,6,2 Hz) 1.67 (s, 3H). ESI-MS m/z 271 $(M+Na)^+$.

Ethyl (2*S*,3*R*)-3-hydroxy-2-[(4-methylphenyl)methyl]hexanoate (5g). ^1H NMR (400 MHz, $CDCl_3$) δ 7.1 (s, 4H); 4.1 (q, 2H); 3.6 (m, 1H); 2.9 (m, 2H); 2.65 (m, 1H); 2.3 (s, 3H); 1.4 (m, 2H); 1.15 (t, 3H); 0.85 (m, 3H) ppm. ESI-MS *m/z* 287 $(M+Na)^+$.

Methyl (2*R*,3*R*)-2-(2-Methyl-2-propen-1-yl)-3-hydroxy-4-methylpentanoate (5h). Oil. ^1H NMR (400 MHz, $CDCl_3$) δ 4.78 (d, 2H), 4.10 (m, 1H), 3.65 (s, 3H), 3.33 (m, 1H), 2.59 (m, 1H), 2.50-2.25 (m, 2H), 1.73 (s, 3H), 1.65 (m, 1H), 0.95 (m, 6H) ppm. ESI-MS m/z 201 $(M+H)^+$.

Methyl (2*R*,3*R*)-2-(2-Methyl-2-propen-1-yl)-3-hydroxy-6,6,6-trifluorohexanoate (5i). Oil. ^1H NMR (400 MHz, $CDCl_3$) δ 4.81 (s, 1H), 4.76 (s, 1H), 3.71 (s, 3H), 3.68 (m, 1H), 2.88 (dd, 1H), 2.67 (m, 1H), 2.50-2.32 (m, 3H), 2.17 (m, 1H), 1.74 (s, 3H), 1.80-1.58 (m, 2H) ppm. ESI-MS m/z 255 $(M+H)^+$.

Methyl (2*R*,3*R*)-2-(2-Methyl-1-propyl)-3-hydroxyhexanoate (5j). Colorless oil (93%). ^1H NMR (300 MHz, $CDCl_3$) δ 3.75 (s, 3H), 3.65 (m, 1H), 2.57 (m, 1H), 2.10 (bs, 1H), 1.80-1.23 (m, 7H), 0.90 (m, 9H) ppm.

Methyl (2*S*,3*R*)-3-cyclopropyl-3-hydroxy-2-cyclohexylmethylpropanoate (5k). Light yellow oil (100%) 5:1 ratio of diastereomers. ^1H NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 3H), 3.68 (s, minor syn diastereomer), 3.0 (m, 1H), 2.65-2.75 (m, 1H), 2.37 (bs, 1H,

OH), 2.80 (bd, 1H), 2.6-2.8 (m, 6H), 1.10-2.25 (m, 4H), 0.8-0.9 (m, 3H), 0.4-0.6 (m, 2H), 0.2-0.3 (m, 2H). ESI-MS m/z 263 $(M+Na)^+$.

Methyl (2*R*,3*R*)-3-Hydroxy-2-[(4-methylcyclohexyl)methyl])-4-methylpentanoate (5l). Oil (70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.7 (s, 3H), 3.3 (m, 1H), 2.8 (m, 1H), 1.8-1.2 (m, 12H), 0.9 (m, 10H) ppm. ESI-MS m/z 279 $(M+Na)^+$.

Methyl (3*R*)-6,6,6-trifluoro-3-hydroxy-2-cyclohexylmethylhexanoate (5m). Oil (55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 3H), 3.65 (m, 1H), 2.58 (m, 1H), 2.5-2.3 (m, 1H), 2.2-2.1 (m, 1H), 1.8-1.6 (m, 8H), 1.43 (m, 1H), 1.3-1.1 (m, 6H).

Methyl (2*R*,3*R*)-2-(2-Methyl-1-propyl)-3-hydroxybutanoate (5n). Oil (96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (m, 1H), 3.69 (s, 3H), 2.51-2.42 (m, 2H), 1.71-1.62 (m, 1H), 1.58-1.48 (m, 1H), 1.38-1.30 (m, 1H), 1.22 (d, 3H), 0.94 (d, J = 6.8 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H) ppm. APCI-MS m/z 175 $(M+H)^+$.

Methyl (2*S*)-2-[(1*R*)-1-hydroxy-2-phenylethyl]-4-methylpentanoate (5o). Light yellow oil (96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4-7.3 (m, 2H), 7.3-7.2 (m, 3H), 3.87 (m, 1H), 3.72 (s, 3H), 2.79 (ABX, 2H, J = 4.8, 14, 43), 2.6-2.5 (m, 2H), 1.8-1.7 (m, 1H), 1.6-1.5 (m, 1H), 1.5-1.4 (m, 1H), 0.94 (d, J = 6.4, 3H), 0.86 (d, J = 6.4, 3H) ppm.

Ethyl (2*S*,3*R*)-3-hydroxy-2-[(4-methylcyclohexyl)methyl]hexanoate (5p). NMR (300 MHz, $CDCl_3$) δ 4.2 (m, 2H), 3.65 (m, 1H), 3.0 (br s, 1H), 2.5 (m, 2H), 1.9-1.2 (m, 18H), 1.0-0.8 (m, 6H) ppm. APCI-MS *m/z* 293 $(M+Na)^+$.

Methyl (2*R*,3*R*)-2-(2-Methyl-1-propyl)-3-hydroxy-4-methylpentanoate (5q). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (s, 3H), 3.30 (m, 1H), 2.70 (m, 1H), 2.50 (d, 1H), 1.78-1.37 (m, 3H), 0.95 (m, 12H) ppm. ESI-MS m/z 203 $(M+H)^+$.

Methyl (2*R*,3*R*)-2-(2-Methyl-1-propyl)-3-hydroxy-6,6,6-trifluorohexanoate (5r). Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 3H), 3.65 (m, 1H), 2.50 (m, 1H), 2.48-2.30 (m, 2H), 2.23-2.07 (m, 1H), 1.70-1.67 (m, 2H), 1.65-1.50 (m, 2H), 1.43-1.37 (m, 1H), 0.96 (dd, 6H) ppm.

Ethyl (2*S*,3*R*)-3-hydroxy-2-[(5-methyl-2-thienyl)methyl]hexanoate (5s). Orange oil (35%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.64 (d, 1H), 6.57 (d, 1H), 4.19 (q, 2H), 3.75 (m, 1H,), 3.17 (m, 2H), 2.74 (m, 1H), 2.57 (m, 1H), 2.46 (s, 3H), 1.45 (m, 4H), 1.26 (t, J = 4.0 Hz, 3H), 0.95 (t, J = 6.8 Hz, 3H) ppm. Anal. ($C_{14}H_{22}O_3S$) C, H, N, S.

Methyl (2*S*,3*R*)-2-(cyclohexylmethyl)-3-hydroxyhexanoate (5t).

Oil (45%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.15 (q, 2H), 3.65 (m, 1H), 2.60 (m, 1H), 2.40 (d, 1H), 1.96-0.94 (m, 20H) ppm.

General procedure for the preparation of N-tetrahydro-2H-pyran-2-yloxyazetidinones 6j-t.

Esters **5j-t** (1.0 eq) were treated with 2.2 eq LiOH (0.5 M) in MeOH:THF:H_2O (3:1:1) at ambient temperature for 24 h until hydrolysis complete by TLC. The crude carboxylate solution was added to excess H_2O and extracted with ether (2x), acidified to pH 1 with 1 N HCl and extracted into ether (3x). The combined ether layers were washed with brine, dried over $MgSO_4$ and filtered and concentrated *in vacuo* to afford the acids as oils (85-95%).

The crude acids were dissolved in ethyl acetate (0.5 M) and cooled in ice and $THPONH_2$ (1.5 eq.) was added all at once followed by DCC (1.05 eq.) in portions over 30 min. After 3-6 h the dicyclohexylurea was removed by filtration and the filtrate washed with 1M $KHSO_4$ (2x), 5% $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide the crude *O*-tetrahydropyran-2-yloxy hydroxamates (Method A; 77-99%). Alternatively, the crude acids (1.0 eq.) along with $THPONH_2$ (1.1-2.0 eq.) were dissolved in DCM (0.5-1M) and treated at 0 °C with EDC (1.2 eq.). After all carboxylic acid was consumed (TLC, 3-12 h) the reaction mixture was washed with 1N HCl, 5% $NaHCO_3$, and brine and dried over $MgSO_4$ to provide the crude *O*-tetrahydropyran-2-yloxy hydroxamates (Method B; 55-97%).

Hydroxamates (1.0 eq.) were dissolved in DCM (0.5M) and pyridine (3.0 eq.) and cooled in ice while methanesulfonyl chloride (1.1 eq.) was added dropwise. After 3-24 h., the reaction mixtures were diluted with DCM, washed with water, 1N HCl, 5% $NaHCO_3$, brine and dried over $MgSO_4$. The crude mesylates were dissolved in acetone (0.5M). Solid K_2CO_3 (3.0 eq.) was added and the suspension was refluxed for 24-48 hours until the mesylate was consumed as monitored by TLC. After cooling to ambient temperature, the reaction mixtures were filtered and the filtrate concentrated to dryness and purified on SiO_2 (Hexanes:EtOAc).

(3*R*,4*S*)-3-(2-Methyl-1-propyl)-4-propyl-1-(2-tetrahydro-2*H*-pyran-2-yloxy)azetidin-2-one (6j). Oil. (91% from **5j**) as a 1:1 mixture of THP diastereomers. ^{1}H NMR (300

MHz, $CDCl_3$) δ 5.20 (m, 0.5H), 5.04 (m, 0.5H), 4.50 (m, 0.5H), 4.27 (m, 0.5H), 4.01-3.89 (m, 1H), 3.68 (m, 1H), 3.05 (m, 1H), 1.92-1.30 (m, 13H), 1.00 (m, 9H) ppm.

(3*R*,4*S*)-3-Cyclohexylmethyl-4-cyclopropyl-1-(2-tetrahydro-2*H*-pyran-2-yloxy)azetidin-2-one (6k). Oil. (32% from **5k**) as a 1:1 mixture of THP diastereomers. ^1H NMR (400 MHz, $CDCl_3$) δ 5.21 (bs, 0.5H), 5.04 (bs, 0.5H), 4.25-4.18 (m, 1H), 3.70-3.60 (m, 1H), 3.20-3.15 (m, 0.5H), 3.10-2.95 (m, 0.5H), 2.95-2.90 (m, 0.5H), 2.76-2.70 (m, 0.5H), 1.8-1.4 (m, 14H), 1.4-1.0 (m, 4H), 1.0-0.8 (m, 2H), 0.7-0.5 (m, 2H), 0.4-0.1 (m, 2H) ppm. ESI-MS m/z 308 $(MH)^+$, 330 $(M+Na)^+$, 224 $[(MH)^+-C_5H_8O)]$.

(3*R*,4*S*)-1-(2-Tetrahydro-2*H*-pyran-2-yloxy)-3-(4-methylcyclohexylmethyl)-4-isopropylazetidin-2-one (6l). White glass. (39% from **5l**) as a mixture of THP and cyclohexyl diastereomers. ^1H NMR (300 MHz, $CDCl_3$) δ 5.3 (bs, 0.5H), 5.1 (bs, 0.5H), 4.35 (m, 0.5H), 4.2 (m, 0.5H), 3.65 (m, 2H); 3.05 (m, 1H); 1.2-2.0 (m, 19H), 1.25 (m, 3H); 0.9 (m, 6H) ppm. ESI-MS m/z 346 $(M+Na)^+$.

(3*R*,4*S*)-3-Cyclohexyl-4-(3,3,3-trifluoropropyl)-1-(2-tetrahydro-2*H*-pyran-2-yloxy)azetidin-2-one (6m). Oil. (50% from **5m**) as a 1:1 mixture of THP diastereomers. ^1H NMR (400 MHz, $CDCl_3$) δ 5.15 (m, 0.5H), 4.95 (m, 0.5H), 4.15 (m, 0.5H), 4.08 (m, 0.5H), 3.95 (m, 0.5H), 3.90 (m, 0.5H), 3.62 (m, 1H), 3.15 (m, 1H), 2.5-2.3 (m, 1H), 2.3-2.1 (m, 1H), 2.0-1.4 (m, 17H), 1.4-1.1 (m, 2H),.1.0-0.8 (m, 2H) ppm.

(3*R*,4*S*)-3-(2-Methyl-1-propyl)-4-methyl-1-(2-tetrahydro-2*H*-pyran-2-yloxy)azetidin-2-one (6n). Oil. (32% from **5n**) as a 1:1 mixture of THP diastereomers. ^1H NMR (400 MHz, $CDCl_3$) δ 5.10 (m, 0.5H), 4.97 (m, 0.5H), 4.18-3.97 (m, 2H), 3.60 (m, 1H), 3.03-2.88 (m, 1H), 1.82-1.50 (m, 8H), 1.30-1.25 (m, 1H), 1.24-1.20 (m, 3H), 0.95 (m, 6H) ppm. APCI-MS m/z 242 $(M+H)^+$.

(3*R*,4*S*)-3-(2-Methyl-1-propyl)-4-methylphenyl-1-(2-tetrahydro-2*H*-pyran-2-yloxy)azetidin-2-one (6o). White solid. (64% from **5o**) as a 1:1 mixture of THP diastereomers. ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.20 (m, 5H), 4.97 (bs, 0.5H), 4.56 (bs, 0.5H), 4.41 (q_{app}, 0.5H), 4.23 (q_{app}, 0.5H), 4.20-4.15 (m, 0.5H), 3.60-3.55 (m, 0.5H), 3.40 (m, 1H), 3.20-3.10 (m, 1H), 3.05 (q_{app}, 0.5H), 2.98-2.90 (m, 1.5H), 1.8-1.3 (m, 9H), 0.95-0.90 (m, 6H) ppm. ESI-MS m/z 340 $(M+Na)^+$.

(3*R*,4*S*)-1-(2-Tetrahydro-2*H*-pyran-2-yloxy)-3-(4-methylcyclohexylmethyl)-4-propylazetidin-2-one (6p). White solid. (50% from **5p**) as a 1:1 mixture of THP

diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.25 (bs, 0.5H), 5.05 (bs, 0.5H), 4.25 (m, 0.5H), 4.15 (m, 0.5H), 3.9 (m, 1H), 3.65 (m, 1H), 3.05 (m, 1H), 1.2-2.0 (m, 22H), 1.0 (m, 6H) ppm. ESI-MS *m/z* 340 $(M+Na)^+$.

(3*R*,4*S*)-3-(2-Methyl-1-propyl)-4-isopropyl-1-(2-tetrahydro-2*H*-pyran-2-yloxy)azetidin-2-one (6q). Oil. (37% from **5q**) as a 1:1 mixture of THP diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.27 (m, 0.5H), 5.06 (m, 0.5H), 4.30 (m, 0.5H), 4.07 (m, 0.5H), 3.61(m, 2H), 3.02 (m, 1H), 2.00-1.58 (m, 9H), 1.38 (m, 1H), 1.10-0.95 (m, 12H) ppm. ESI-MS m/z 270 $(M+H)^+$.

(3*R*,4*S*)-3-(2-Methyl-1-propyl)-4-(3,3,3-trifluoropropyl)-1-(2-tetrahydro-2*H*-pyran-2-yloxy)azetidin-2-one (6r). Oil. (7% from **5r**) as a 1:1 mixture of THP diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.10 (m, 0.5H), 4.98 (m, 0.5H), 4.20-3.88 (m, 2H), 3.60 (m, 1H), 3.10 (m, 1H), 2.5-2.10 (m, 2H), 2.0 (m, 10H), 1.37-1.20 (m, 1H), 0.95 (m, 6H) ppm. ESI-MS m/z 346 $(M+Na)^+$.

(3*R*,4*S*)-3-[(5-Methyl-2-thienyl)methyl]-4-propyl-1-(2-tetrahydro-2*H*-pyran-2-yloxy)azetidin-2-one (6s). Yellow oil (65% from **5s**) as a 1:1 mixture of THP diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.68 (br d, 1H), 6.59 (br d, 1H), 5.24 (s, 0.5H), 5.07 (s, 0.5H), 4.28 (m, 0.5H,), 4.06 (m, 1.5H), 3.29 (m, 3H), 3.02 (m, 1H), 2.46 (s, 3H), 1.73 (m, 8H), 1.79 (m, 1H), 1.32 (m, 1H), 0.98 (t, 1.5H), 0.97 (t, 1.5H) ppm. Anal. ($C_{17}H_{25}O_3SN$) C, H, N, S.

(3*R*,4*S*)-3-Cyclohexylmethyl-4-propyl-1-(2-tetrahydro-2*H*-pyran-2-yloxy)azetidin-2-one (6t). Oil. (54% from **5t**) as a 1:1 mixture of THP diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.18 (m, 0.5H), 5.01 (m, 0.5H), 4.23 (m, 0.5H), 4.14 (m, 0.5H), 3.90 (m, 1H), 3.63 (m, 1H), 3.02 (m, 1H), 1.85-0.93 (m, 26H) ppm.

General procedure for the preparation of β-tetrahydro-2*H*-pyran-2-yloxyamino acids 7j-t.

Azetidinones **6j-t** (1.0 eq.) were dissolved in dioxane (0.3M) and treated with 3N NaOH solution (3.0 eq.; final [NaOH] = 1M). After stirring at 25 °C (or 40 °C in the case of hindered azetidinones **6k**, **6l**, and **6q**) for 24 h, the reaction mixtures were acidified with 1N HCl or solid $NaHSO_4$, extracted with ether, washed with brine and dried ($MgSO_4$). Filtration and concentration *in vacuo* provided the crude acids that were taken up in pyridine (1M) and cooled to 0 °C. Acetic formic anhydride (3-5 eq) was added

dropwise. After 2h the reaction mixture was allowed to warm to ambient temperature and concentrated *in vacuo*. The resulting crude oil was taken up in ether, washed with aqueous 1N $NaHSO_4$ (2x), water, brine and dried ($MgSO_4$). Filtration and concentration provided the carboxylic acids **7j-t**.

Acid **7n** was isolated and characterized as its pentafluorophenyl ester and used as such in the subsequent amide coupling step. Thus **7n** (1 eq.) was dissolved in EtOAc (0.25-0.5M) along with pentafluorophenol (1.0 eq). To the stirred solution at 0 °C was added DCC (1.0 eq.). After 16 h, the reaction mixture was filtered and the concentrated filtrate purified on SiO_2 (Hexanes:EtOAc 4:1) to provide the pentafluorophenyl ester of **7n**.

(2*R*,3*R*)-3-[Formyl(tetrahydro-2*H*-pyran-2-yloxy)amino]-2-isobutylhexanoic acid (7j). Oil (90% from **6j**). 1:1 Mixture of THP diastereomers and 3° amide rotamers. ^1H NMR (300 MHz, $CDCl_3$) δ 8.80 (bs, 1H), 4.85 (bs, 0.5H), 4.75 (bs, 0.5H), 3.95 (m, 1H), 3.60 (m, 1H), 3.19 (m, 0.5H), 2.87 (m, 0.5H), 3.05 (m, 1H), 1.95-1.12 (m, 13H), 0.91 (m, 9H) ppm.

(2*R*,3*S*)-2-(Cyclohexylmethyl)-3-cyclopropyl-3-[formyl(tetrahydro-2*H*-pyran-2-yloxy)amino]propanoic acid (7k). Oil (51% from **6k**). 1:1 Mixture of THP diastereomers and 3° amide rotamers. ^1H NMR (400 MHz, CD_3OD) δ 8.45 (s, 0.25H), 8.42 (s, 0.25H), 8.41 (s, 0.25H), 8.29 (s, 0.25H), 5.16 (m, 0.25H), 5.10 (m, 0.25H), 5.00 (m, 0.25H), 4.92 (m, 0.25H), 4.10 (m, 0.25H), 3.95 (m, 0.75H), 3.7-3.5 (m, 2H), 3.22-2.85 (m, 2H), 2.0-1.4 (m, 8H), 1.4-1.1 (m, 7H), 1.0-0.7 (m, 4H), 0.5-0.4 (m, 2H), 0.4-0.2 (m, 2H) ppm. ESI-MS (neg. ion) m/z 352 $(M-H)^+$; (pos. ion) 376 $(M+Na)^+$, 354 $(M+H)^+$, 270 $(MH-C_5H_8O)^+$.

(2*R*,3*S*)-3-[Formyl(tetrahydro-2*H*-pyran-2-yloxy)amino]-5-methyl-2-[(4-methylcyclohexyl)methyl]hexanoic acid (7l). Foam (60% from **6l**). 1:1 Mixture of THP diastereomers and 3° amide rotamers. ^1H NMR (400 MHz, $CDCl_3$) δ 8.5 (s, 0.5H), 8.0 (s, 0.5H), 5.05 (bs, 0.5H), 4.9 (bs, 0.5H), 4.3 (s, 0.5H), 4.2 (s, 0.5H), 3.95 (m, 1H); 3.6 (m, 2H); 3.1 (s, 0.5H), 2.9 (s, 0.5H), 2.15 (s, 0.5H), 2.0 (s, 0.5H), 1.0-2.0 (m, 19H); 0.9 (m, 9H). ESI-MS *m/z* 370 $(M+H)^+$, 392 $(M+Na)^+$.

(2*R*,3*S*)-2-(Cyclohexylmethyl)-6,6,6-trifluoro-3-[formyl(tetrahydro-2*H*-pyran-2-yloxy)amino]hexanoic acid (7m). Foam (50% from **6m**) as a 1:1 Mixture of THP

diastereomers and 3° amide rotamers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 0.7H), 8.03 (m, 0.3H), 5.05 (m, 0.3H), 4.80 (m, 0.7H), 4.38 (m, 1H), 3. 95 (m, 1H), 3.61 (m, 1H), 3.0-2.8 (m, 1H), 2.3-1.9 (m, 2H), 1.9-1.5 (m, 16H), 1.5-1.0 (m, 3H), 1.0-0.7 (m, 2H) ppm.

Pentafluorophenyl ester of (2*R*)-2-{(1*S*)-1-[formyl(tetrahydro-2*H*-pyran-2-yloxy)amino]ethyl}-4-methylpentanoic acid (7n). Oil (63% from **6n**). 1:1 Mixture of THP diastereomers and 3° amide rotamers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 4.85 (m, 1H), 4.70-4.59 (m, 1H), 4.06-3.83 (m, 1H), 3.63-3.59 (m, 1H), 3.27-3.03 (m, 1H), 1.96-1.20 (m, 12H), 1.00-0.95 (m, 6H) ppm. APCI-MS m/z 454 $(M+H)^+$.

(2*R*)-2-{(1*S*)-1-[Formyl(tetrahydro-2*H*-pyran-2-yloxy)amino]-2-phenylethyl}-4-methylpentanoic acid (7o). Oil (86% from **6o**). 1:1 Mixture of THP diastereomers and 3° amide rotamers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 0.5H), 8.25 (s, 0.5H), 7.3-7.15 (m, 5H), 5.01 (m, 0.5H), 4.85 (m, 0.5H), 4.63 (m, 0.5H), 4.42 (m, 0.5H), 4.28 (m, 0.5H), 4.10 (m, 0.5H), 3.9 (m, 0.5H), 3.65 (m, 0.5H), 3.4 (m, 0.5H), 3.2 (m, 0.5H), 3.1 (m, 1H), 2.8 (m, 1H), 1.8-1.4 (m, 9H), 0.92 (m, 6H). APCI-MS *m/z* (neg. ion) 362 $(M-H)^+$.

(2*R*,3*S*)-3-[Formyl(tetrahydro-2*H*-pyran-2-yloxy)amino]-2-[(4-methylcyclohexyl)methyl]hexanoic acid (7p). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.5 (s, 0.5H), 7.95 (s, 0.5H) 5.0 (s, 0.5H), 4.8 (s, 0.5H), 4.35 (m, 1H), 3.95 (m, 1H), 3.6 (m, 1H); 2.9 (m, 0.5H) 2.7 (m, 0.5H); 1.2-2.0 (m, 17H), 0.95 (m, 6H) ppm. ESI-MS *m/z* (pos. ion) 392 $(M+Na)^+$, (neg. ion) 368 $(M-H)^+$.

(2*R*,3*S*)-3-[Formyl(tetrahydro-2*H*-pyran-2-yloxy)amino]-2-isobutyl-6-methylpentanoic acid (7q). Oil (91% from **6q**). 1:1 Mixture of THP diastereomers and 3° amide rotamers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (m, 1H), 8.50 (m, 0.5H), 8.00 (m, 0.5H), 5.05 (m, 0.5H), 4.90 (m, 0.5H), 4.38-4.16 (m, 1H), 3.97 (m, 1H), 3.60 (m, 1H), 3.10 (m, 1H), 2.90 (m, 1H), 2.20-1.98 (m, 2H), 1.90-1.10 (m, 7H), 1.05-0.80 (m, 12H) ppm. ESI-MS *m/z* 316 $(M+H)^+$.

(2*R*,3*S*)-6,6,6-Trifluoro-3-[formyl(tetrahydro-2*H*-pyran-2-yloxy)amino]-2-isobutylhexanoic acid (7r). Oil (93% from **6r**). 1:1 Mixture of THP diastereomers and 3° amide rotamers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (m, 0.7H), 8.65 (m, 0.3H), 5.03 (s, 0.3H), 4.82 (s, 0.7H), 4.42-4.30 (m, 1H), 4.03-3.95 (m, 1H), 3.61-3.57 (m, 1H); 3.30-

3.20 (m, 1H), 2.48-2.11 (m, 2H), 1.84-1.42 (m, 11H), 0.94 (m, 6H) ppm. ESI-MS *m/z* 370 $(M+H)^+$; 368 $(M-H)^+$.

(2*R*,3*S*)-3-[Formyl(tetrahydro-2*H*-pyran-2-yloxy)amino]-2-[(5-methyl-2-thienyl)methyl]hexanoic acid (7s). White foam (79% from **6s**). 1:1 Mixture of THP diastereomers and 3° amide rotamers. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.1 (br, 1H), 8.58 (m, 0.7H), 8.07 (s, 0.3H), 6.59 (m, 1H), 6.56 (br s, 1H), 5.14 (m, 0.3H), 4.89 (s, 0.7H), 4.80 (s, 0.3H,), 4.51 (m, 0.7H), 4.04 (m, 0.7H), 3.68 (m, 1.3H), 3.13 (m, 3H), 2.45 (s, 3H), 1.96 (m, 2H), 1.66 (m, 6H), 1.37 (m, 2H), 0.95 (m, 1.5H), 0.94 (m, 1.5H) ppm. ESI-MS (LC-MS) (neg. ion) *m/z* 368 $(M-H)^+$.

(2*R*,3*S*)-2-(Cyclohexylmethyl)-3-[formyl(tetrahydro-2*H*-pyran-2-yloxy)amino]hexanoic acid (7t). White foam (75% from **6t**). 1:1 Mixture of THP diastereomers and 3° amide rotamers. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.52 (m, 0.7H), 7.99 (m, 0.3H), 5.05 (m, 0.3H), 4.81 (m, 0.7H), 4.38 (m, 1H), 3.96 (m, 1H), 3.57 (m, 1H), 3.0-2.6 (m, 1H), 2.0-1.0 (m, 22H), 0.90 (m, 3H), 0.87 (m, 1H) ppm. ESI-MS (LC-MS) (pos. ion) *m/z* 378 $(M+Na)^+$; (neg. ion) *m/z* 354 $(M-H)^+$.

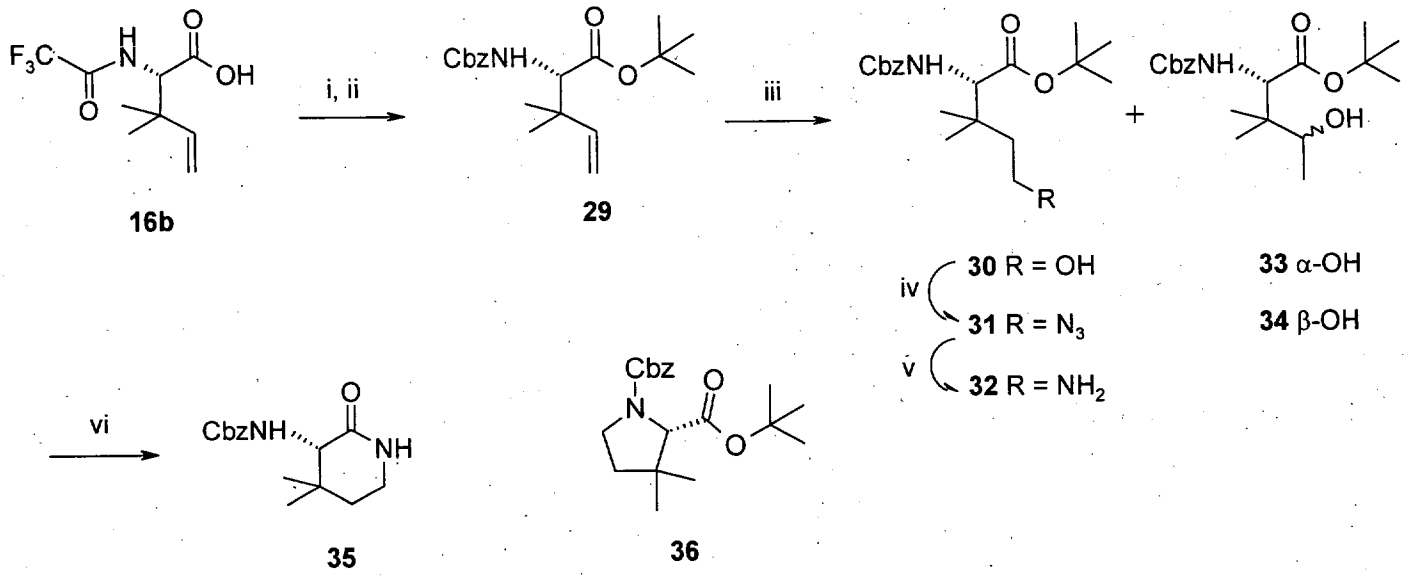
Synthesis of β,β-dimethylornithine *tert*-butyl ester.

The product of an asymmetric Kazmeir Claisen rearrangement, (2*S*)-3,3-Dimethyl-2-[(trifluoroacetyl)amino]-4-pentenoic acid[i] (**16b**; 74.5% e.e.; Scheme S1) was treated sequentially with aqueous NaOH, then CbzCl. A single recrystalization of the Cbz amino acid as the (*S*) α-methylbenzylamine salt followed by acidification resulted in (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3,3-dimethyl-4-pentenoic acid with an e.e. of 95.6%. The acid was esterified with dimethylformamide di *tert*-butyl acetal to afford **29**. Esterification as the *tert*-butyl ester was found to be crucial to obtaining good yields in the subsequent hydroboration. Reaction of alkene **29** with sterically demanding hydroborating reagents was slow and provided low yields of desired alcohol **30**. Hydroboration with borane-THF at 0 °C followed by treatment with H_2O_2 in pH 7.0 phosphate buffer provided **30** (52%) along with isomeric 2° alcohols **33** and **34** in a 7.4:1.0:1.7 ratio, respectively. The relative configurations of 2° alcohols **33** and **34** were determined by ^{1}HNMR nOe analysis of the corresponding lactones (TFA). Conversion of **30** to the azide by activation (methanesulfonyl chloride, pyridine) and azide

displacement (NaN_3, DMF) provided **31** (90%) accompanied by 8-10% pyrrolidine **36**, the product of cyclization of the intermediate mesylate. Reduction of **31** with 1,3-propanedithiol and TEA[ii] gave a 1° amine (**32**) that was unstable to subsequent derivatization and underwent significant cyclization to piperidone **35** upon treatment with either dimethyl methylsulfonyldithioimidocarbonate or 3,5-dimethyl-1*H*-pyrazole-1-carboxamidine nitrate. Amine **32** could however be derivatized at low temperature with more reactive reagents.*

* For example, coupling of **32** with picolinic acid imidazolide at 0 °C (prepared by the treatment of picolinic acid with carbonyldiimidazole) resulted in a 77% isolated yield of the corresponding picolinic amide.

Scheme S1[a]



[a]Reagents: (i) NaOH, H_2O, 80 °C, 1 h, then CbzCl, 0-23 °C, 30 min; (ii) $(t\text{-BuO})_2CHNMe_2$, toluene, 80 °C, 1 h; (iii) Borane-THF, 0 °C, 2 h, then H_2O_2, pH 7.0, **30** (52%), **33** (7%), **34** (12%); (iv) *a*. MsCl, pyridine, DCM, 0 °C, 12 h, *b*. NaN_3, DMF, 40 °C, 12 h; (v) 1,3-Propanedithiol, MeOH, TEA, RT, 72 h; (vi) TFA, DCM.

***tert*-Butyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3,3-dimethyl-4-pentenoate (29).** Acid **16b** (7.00 g, 29.3 mmol) was dissolved in 30 mL 2.0N NaOH solution and heated at 80 °C for 1 h. The solution was cooled in ice and additional 2.0N NaOH solution (30 mL) was added followed by benzyl chloroformate (5.5 g, 32 mmol, 4.6 mL). The reaction mixture was stirred at 0 °C for 30 min. then allowed to warm to ambient temperature over an additional 30 min. during which tike the reaction mixture became homogeneous. The solution was added to water and basified with additional NaOH until homogeneous again and extracted with ether (2x). The aqueous solution was acidified to pH 1 with 6N HCl and extracted with ether (3x). The combined organic layers were washed with brine, dried over $MgSO_4$/Norit and filtered through Celite to provide (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3,3-dimethyl-4-pentenoic acid as a light yellow oil (8.24 g, 29.7 mmol (100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.4-9.0 (bs, 1H), 7.34 (m, 5H), 5.82 (AB, J=16, 13.2Hz, 1H), 5.24 (d, J=9.6Hz, 1H), 5.09 (m, 4H), 4.22 (d, J=9.6Hz, 1H), 1.14 (s, 3H), 1.12 (s, 3H) ppm. ESI-MS *m/z* 300 $(M+Na)^+$.

The acid was dissolved in 100 mL dry toluene and warmed to 80 °C and dimethylformamide di-*tert*-butyl acetal (28.8 g, 141 mmol) was added dropwise over 30 min. The reaction solution was allowed to stand at 80 °C for a further 30 min. then allowed to cool to ambient temperature. The solution was diluted with ether and washed with water (2x), 1N HCl, 5% $NaHCO_3$ and brine and dried over $MgSO_4$. The mixture was filtered and concentrated and the resulting oil purified on SiO_2 (hexanes:EtOAc 8:1) to afford **29** as a clear oil (7.00 g, 21.0 mmol, 72% from **16b**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 5H), 5.73 (AB, J=13, 16.8 Hz, 1H), 5.12 (bd, J=8.8 Hz, 1H), 5.0-4.9 (m, 4H), 3.99 (d, J=9.2 Hz, 1H), 1.34 (s, 9H), 0.99 (s, 3H), 0.97 (s, 3H) ppm. ESI-MS *m/z* 356 $(M+Na)^+$.

***tert*-butyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-5-hydroxy-3,3-dimethylpentanoate (30).** To a 0 °C solution of alkene **29** (7.00 g, 21.0 mmol) in anhydrous THF (35 mL) was added dropwise over 20 min. a solution of borane in THF (20.4 mL, 21.0 mmol, 1.03 M). After a further 1.5 h excess borane was quenched by the cautious addition of pH 7.00 phosphate buffer (ca. 50 mL) at 0 °C followed by 42 mL of 30% H_2O_2 and the mixture was allowed to warm to ambient temperature overnight with stirring. The mixture was extracted with ether (3x) and washed with saturated $Na_2S_2O_5$ solution (4x),

water, brine, and dried ($MgSO_4$). Purification on SiO_2 (hexanes:EtOAc 2:1) provided **33** (0.670 g, 1.91 mmol, 9.1%), **34** (clear oil, 0.857 g, 2.44 mmol, 12%) and the desired primary alcohol **30** (3.83 g, 10.9 mmol, 52%).

30 (white glass): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 5H), 5.74 (bd, J=9.2 Hz, 1H), 5.09 (m, 2H), 4.26 (d, J=9.6, 1H), 3.74 (m, 2H), 2.17 (m, 1H), 1.65 (m, 1H), 1.50 (m, 1H), 1.45 (s, 9H), 1.00 (s, 3H), 0.96 (s, 3H) ppm. ESI-MS *m/z* 374 $(M+Na)^+$.

33 (white glass): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.68 (bd, J=8.8 Hz, 1H), 5.10 (s, 2H), 4.30 (d, J=10.4, 1H), 3.70 (d, J=4.8 Hz, 1H), 3.58 (m, 1H), 1.47 (s, 9H), 1.09 (d, J=6.4 Hz, 3H), 0.96 (s, 3H), 0.78 (s, 3H) ppm. ESI-MS *m/z* 352 $(M+H)^+$, 374 $(M+Na)^+$.

34 (clear oil): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 5H), 5.33 (m, 1H), 5.10 (m, 3H), 4.31 (d, J=10.4 Hz, 1H), 3.65 (m, 1H), 2.44 (d, J=5.2 Hz, 1H), 1.54 (s, 9H), 1.15 (d, J=6.4 Hz, 3H), 0.94 (s, 3H), 0.84 (s, 3H) ppm. ESI-MS *m/z* 352 $(M+H)^+$, 374 $(M+Na)^+$.

***tert*-butyl (2*S*)-5-azido-2-{[(benzyloxy)carbonyl]amino}-3,3-dimethylpentanoate (31).** Methanesulfonyl chloride (1.35 g, 11.8 mmol, 0.915 mL) was added dropwise to 0 °C solution of alcohol **30** (3.78 g, 10.7 mmol) and pyridine (2.6 mL, 32.3 mmol) in DCM (12 mL). After 20 h at 4 °C the solution was washed with 1 N HCl and brine and dried (MgSO4). Filtration and concentration provided the crude mesylate which was taken up in 20 mL dry DMF and heated at 40 °C with LiN_3 (1.58 g, 32.3 mmol). After 3 h the volatiles were removed under high vacuum and the resulting oil was partitioned between water and ether. The layers were separated and the aqueous phase was extracted with additional ether (3x). The combined ether layers were dried ($MgSO_4$) and purified on SiO_2 (hexanes:EtOAc 9:1 to 8:1 to 4:1) to provide azide **31** (3.66 g, 9.72 mmol, 91%) followed by a small amount of 2-*tert*-butyl 1-phenyl (2*S*)-3,3-dimethyl-1,2-pyrrolidinedicarboxylate (**36**, 0.30 g, 0.90 mmol, 8.4%).

31 (clear oil): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.35 (bd, J=9.2 Hz, 1H), 5.09 (AB, J=12, 17.6, 2H), 4.11 (d, J=9.6 Hz, 1H), 3.35 (m, 2H), 1.6 (m, 2H), 1.46 (s, 9H), 0.96 (s, 3H), 0.95 (s, 3H). ESI-MS *m/z* 377 $(M+H)^+$, 399 $(M+Na)^+$.

36 (clear oil): ^{1}H NMR (400 MHz, $CDCl_3$) (carbamate rotamers) δ 7.31 (m, 5H), 5.11 (m, 2H), 3.83 (s, 0.5H), 3.78 (s, 0.5H), 3.65 (m, 1H), 3.50 (m, 1H), 1.90 (m, 1H), 1.6 (m,

1H), 1.45 (s, 4.5H), 1.32 (s, 4.5H), 1.12 (s, 3H), 1.07 (s, 1.5H), 1.06 (s, 1.5H). ESI-MS *m/z* 334 $(M+H)^+$, 356 $(M+Na)^+$.

***tert*-butyl (2*S*)-5-amino-2-{[(benzyloxy)carbonyl]amino}-3,3-dimethylpentanoate (32).** Azide **31** (0.366 g, 0.973 mmol) was dissolved in MeOH (5 mL) and TEA (0.3 mL). 1,3-Propanedithiol (0.210 mg, 1.95 mmol, 0.20 mL) was added and the reaction mixture was stirred for 72 h. The mixture was purified on Dowex $50H^+$ resin, eluting with MeOH followed by 5% ammonium hydroxide in MeOH to provide **32** as a clear oil (0.27 g, 0.771 mmol, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 5H), 6.20 (bd, J=9.6 Hz, 1H), 5.12 (m, 2H), 4.09 (d, J=9.6 Hz, 1H), 2.75 (m, 2H), 1.51 (bs, 2H), 1.45 (s, 9H), 0.96 (s, 3H), 0.95 (s, 3H). ESI-MS *m/z* 350 $(M+H)^+$, 295 $(MH-C_4H_8)^+$.

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