Electronic Supplementary Material (ESI) for Chemical Communications

Supporting Information

Rational Hopping of a Peptidic Scaffold into Non-Peptidic Scaffolds: Structurally Novel Potent Proteasome Inhibitors Derived from a Natural Product, Belactosin A

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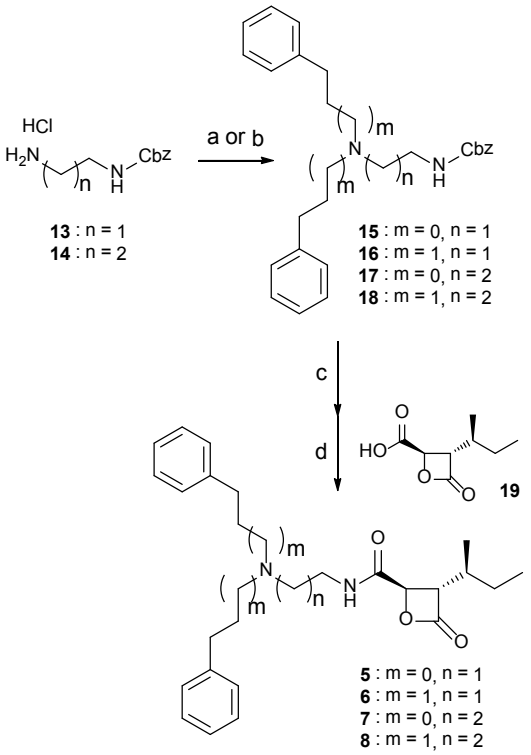
General methods and materials

^{1}H-NMR spectra were recorded in $CDCl_3$ at ambient temperature unless otherwise noted, at 400 or 500 MHz, with TMS as an internal standard. ^{13}C NMR spectra were recorded in $CDCl_3$ at ambient temperature unless otherwise noted, at 100 or 125 MHz. Silica gel column chromatography was performed with silica gel 60 N (spherical, neutral, 63-210 μm, Kanto Chemical Co., Inc.). Flash column chromatography was performed with silica gel 60 N (spherical, neutral, 40-50 μm, Kanto Chemical Co., Inc.). Celite 545 was purchased from Kanto Chemical Co., Inc. $Pd(OH_2)/C$ was purchased from TCI. Combustion analysis was performed to confirm ≥95% sample purity (within ±0.4% of the calculated value).

Synthetic procedures for 5-8

Scheme S1. Synthesis of amine-type targets **5-8**[a]



[a]Reagents and conditions: (a) phenylacetaldehyde, $NaBH_3CN$, MeOH, 96% for **15**, 86% for **17**; (b) benzylacetaldehyde, $NaBH_3CN$, MeOH, quant. for **16**, 90% for **18**; (c) H_2, $Pd(OH)_2/C$, MeOH; (d) **19**, PivCl, Et_3N, CH_2Cl_2, 0 °C to rt, yields were as follows (2 steps), 90% for **5**, quant. for **6**, 83% for **7**, 67% for **8**.

General procedure for the preparation of **15-18**

To a solution of the hydrochloride salt of a primary amine (1.0 equiv) in MeOH (0.1 M) was added aldehyde (5.0 equiv). After 30 min at rt, $NaBH_3CN$ (4.5 equiv) was added and the resulting mixture was stirred for 28 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in $CHCl_3$, washed with sat. $NaHCO_3$, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography to yield the corresponding tertiary amine.

benzyl (2-(diphenethylamino)ethyl)carbamate **15**

Amine **15** (860.2 mg, 2.14 mmol, 96%) was obtained as a colorless oil by the reaction of amine **13** (515 mg, 2.23 mmol) and phenylacetaldehyde. Purification was conducted by silica gel column chromatography (*n*-hexane/ AcOEt 10:3-3:1). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.43-7.02 (m, 15 H, aromatic), 5.06 (br, 2H, Cbz CH_2), 4.82 (br, 1H, carbamate NH), 3.10 (td, *J* = 11.2, 5.4 Hz, 2H, C$\underline{H}_2$NH), 2.78-2.63 (m, 8H, benzyl CH_2 and BnCH_2), 2.58 (t, *J* = 5.4 Hz, 2H, C$\underline{H}_2$CH_2NH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.3, 140.4, 136.7, 128.7, 128.4, 128.4, 128.0, 127.9, 126.0, 66.4, 55.5, 52.6, 38.4, 33.6; LRMS (ESI) *m/z* 403.24 [$(M+H)^+$]; HRMS (ESI) calcd for $C_{26}H_{31}N_2O_2$: 403.2380 [$(M+Na)^+$], found: 403.2379.

benzyl (2-(bis(3-phenylpropyl)amino)ethyl)carbamate **16**

Amine **16** (258 mg, 0.599 mmol, quant.) was obtained as a colorless oil by the reaction of amine **13** (135 mg, 0.587 mmol) and 3-phenylpropionaldehyde. Purification was conducted by silica gel column chromatography (*n*-hexane/ AcOEt 3:2). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.39-7.09 (m, 15H, aromatic), 5.25 (br, 1H, carbamate NH), 5.08 (br, 2H, Cbz CH_2), 3.20 (dd, *J* = 11.3, 5.4 Hz, 2H, C$\underline{H}_2$NH), 2.56 (t, *J* = 7.7 Hz, 4H, benzyl CH_2 or BnCH_2C$\underline{H}_2$N), 2.51 (t, *J* = 5.9 Hz, 2H, C$\underline{H}_2$CH_2NH), 2.44 (t, *J* = 7.2 Hz, 4H, BnCH_2C$\underline{H}_2$N), 1.71 (tt, *J* = 7.7, 7.2 Hz, 4H, Bn$C\underline{H}_2$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.3, 142.0, 136.6, 128.4, 128.3, 128.0, 128.0, 125.7, 66.5, 53.2, 53.0, 38.5, 33.6, 28.7; LRMS (ESI) *m/z* 431.27 [$(M+H)^+$]; HRMS (ESI) calcd for $C_{28}H_{35}N_2O_2$: 431.2693 [$(M+H)^+$], found: 431.2689.

benzyl (3-(diphenethylamino)propyl)carbamate **17**

Amine **17** (762 mg, 1.83 mmol, 86%) was obtained as a colorless oil by the reaction of amine **14** (518 mg, 2.12 mmol) and phenylacetaldehyde. Purification was conducted by silica gel column chromatography (*n*-hexane/ AcOEt 3:2). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.39-7.07 (m, 15H, aromatic), 5.64 (br, 1H, carbamate NH), 5.08 (s, 2H, Cbz CH_2), 3.19 (td, *J* = 5.9, 5.9 Hz, 2H, C$\underline{H}_2$NH), 2.79-2.64 (m, 8H, benzyl CH_2 and BnCH_2), 2.58 (t, *J* = 6.3 Hz, 2H, C$\underline{H}_2$CH_2CH_2NH), 1.61 (tt, *J* = 6.3, 5.9 Hz, 2H, C$\underline{H}_2$CH_2NH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.3, 140.3, 136.8, 128.7, 128.4, 128.3, 128.0, 127.9, 126.0, 66.3, 55.7, 52.5, 40.4, 33.5, 26.6; LRMS (ESI) *m/z* 417.25 [$(M+H)^+$]; HRMS (ESI) calcd for $C_{27}H_{33}N_2O_2$: 417.2537 [$(M+H)^+$], found: 417.2533.

benzyl (3-(bis(3-phenylpropyl)amino)propyl)carbamate **18**

Amine **18** (819 mg, 1.84 mmol, 90%) was obtained as a colorless oil by the reaction of amine **14** (503 mg, 2.06 mmol) and 3-phenylpropionaldehyde. Purification was conducted by silica gel column chromatography (*n*-hexane/ AcOEt 5:1-2:1-1:2). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.37-7.09 (m, 15H, aromatic), 6.16 (br, 1H, carbamate NH), 5.07 (s, 2H, Cbz CH_2), 3.27 (dd, *J* = 11.5, 5.7 Hz, 2H, C$\underline{H}_2$NH), 2.58 (t, *J* = 7.4 Hz, 4H, benzyl CH_2 or BnCH_2C$\underline{H}_2$N), 2.47 (t, *J* = 6.3 Hz, 2H, C$\underline{H}_2$CH_2CH_2NH), 2.41 (t, *J* = 7.4 Hz, 4H, benzyl CH_2 or BnCH_2C$\underline{H}_2$N), 1.73 (tt, *J* = 7.4, 7.4 Hz, 4H, BnCH_2), 1.65-1.53 (m, 2H, C$\underline{H}_2$CH_2NH); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 156.3, 142.0, 136.8, 128.3, 128.2, 127.9, 127.8, 125.7, 66.3, 53.4, 53.3, 40.9, 33.6, 28.5, 26.1; LRMS (ESI) *m/z* 445.28 [$(M+H)^+$]; HRMS (ESI) calcd for $C_{29}H_{37}N_2O_2$: 445.2850 [$(M+H)^+$], found: 445.2847.

General procedure for the preparation of target compounds **5-8**

To a solution of the Cbz-protected amine (1.0 equiv) in MeOH (0.1 M) was added $Pd(OH)_2/C$ (50% w/w of the substrate). The flask was purged with hydrogen and the reaction mixture was stirred under an atmosphere of hydrogen (balloon pressure) for 6 h. The reaction mixture was filtered through a Celite pad and the filtrate was concentrated *in vacuo* to give the corresponding primary amine.

To a solution of carboxylic acid **19**[1] (2.5 equiv) in DCM (0.1 M) was added triethylamine (2.5 equiv) and PivCl (2.3 equiv) at 0 °C. After 30 min at 0 °C, the reaction mixture was used as a solution of the corresponding acid anhydride in DCM.

To a solution of the aforementioned amine in DCM (0.1 M) was added triethylamine (1.5 equiv) and a solution of the acid anhydride in DCM at 0 °C. After 5 min at 0 °C, the reaction mixture was warmed to rt and stirred for 18 h. The reaction mixture was diluted with DCM, washed with sat. $NaHCO_3$, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography to yield the corresponding target compound.

Target compound **5**

The crude product was purified by silica gel column chromatography (*n*-hexane/ AcOEt 2:1) to yield target compound **5** (77.8 mg, 0.184 mmol, 2 steps 90%) as a colorless oil. $[\alpha]^{25}_D$ -3.30 (*c* 1.31, CH_2Cl_2) δ 7.34-7.11 (m, 10H, aromatic), 6.46 (br, 1H, amide NH), 4.47 (d, *J* = 4.6 Hz, 1H, NHCOC<u>H</u>), 3.52 (dd, *J* = 8.0, 4.6 Hz, 1H, OCOCH), 3.30-3.20 (m, 1H, C<u>H</u>$_2$NH), 3.18-3.08 (m, 1H, C<u>H</u>$_2$NH), 2.77 (t, *J* = 7.4 Hz, 4H, benzyl CH_2 or $BnCH_2$), 2.70 (t, *J* = 7.4 Hz, 4H, benzyl CH_2 or $BnCH_2$), 2.62 (t, *J* = 5.7 Hz, 2H, C<u>H</u>$_2$CH$_2$NH), 2.02-1.91 (m, 1H, *sec*-butyl CH), 1.71-1.60 (m, 1H, *sec*-butyl CH_2), 1.37-1.23 (m, 1H, *sec*-butyl CH_2), 1.06 (d, *J* = 6.9 Hz, 3H, *sec*-butyl CH_3), 0.94 (dd, *J* = 7.4, 7.4 Hz, 3H, *sec*-butyl CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 169.3, 167.6, 140.2, 128.7, 128.5, 126.1, 70.6, 62.6, 55.7, 52.4, 36.8, 33.8, 33.7, 26.6, 16.3, 11.0; LRMS (ESI) *m/z* 423.26 [$(M+H)^+$]; HRMS (ESI) calcd for $C_{26}H_{35}N_2O_3$: 423.2642 [$(M+H)^+$], found: 423.2642.

Target compound **6**

The crude product was purified by silica gel column chromatography (*n*-hexane/ AcOEt 3:2) to yield target compound **6** (59.6 mg, 0.132 mmol, 2 steps quant.) as a colorless oil. $[\alpha]^{25}_D$ -5.95 (*c* 0.46, CH_2Cl_2); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.31-7.25 (m, 4H, aromatic), 7.21-7.14 (m, 6H, aromatic), 6.94 (br, 1H, amide NH), 4.57 (d, *J* = 4.6 Hz, 1H, NHCOC<u>H</u>), 3.55 (dd, *J* = 7.4, 4.6 Hz, 1H, OCOCH), 3.37-3.21 (m, 2H, C<u>H</u>$_2$NH), 2.60 (t, *J* = 7.4 Hz, 4H, benzyl CH_2 or $BnCH_2C\underline{H}_2N$), 2.56 (dd, *J* = 6.3, 5.7 Hz, 2H, C<u>H</u>$_2$CH$_2$NH), 2.47 (t, *J* = 7.4 Hz, 4H, benzyl CH_2 or $BnCH_2C\underline{H}_2N$), 2.02-1.91 (m, 1H, *sec*-butyl CH), 1.73 (tt, *J* = 7.4, 7.4 Hz, 4H, $BnCH_2$), 1.70-1.59 (m, 1H, *sec*-butyl CH_2), 1.35-1.25 (m, 1H, *sec*-butyl CH_2), 1.06 (d, *J* = 6.9 Hz, 3H, *sec*-butyl CH_3), 0.93 (dd, *J* = 7.4, 7.4 Hz, 3H, *sec*-butyl CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 169.2, 167.8, 141.9, 128.3, 128.3, 125.8, 70.7, 62.9, 53.2, 52.3, 36.7, 33.8, 33.5, 28.6, 26.6, 16.3, 11.0; LRMS (ESI) *m/z* 451.30 [$(M+H)^+$]; HRMS (ESI) calcd for $C_{28}H_{39}N_2O_3$: 451.2955 [$(M+H)^+$], found: 451.2957.

Target compound **7**

The crude product was purified by silica gel column chromatography (*n*-hexane/ AcOEt 3:2) to yield target compound **7** (51.8 mg, 0.119 mmol, 2 steps 83%) as a colorless oil. $[\alpha]^{25}_D$ -5.00 (*c* 0.56, CH_2Cl_2); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.00 (br, 1H, amide NH), 7.33-7.15 (m, 10H, aromatic), 4.53 (d, *J* = 4.6 Hz, 1H, NHCOC<u>H</u>), 3.55 (dd, *J* = 7.4,

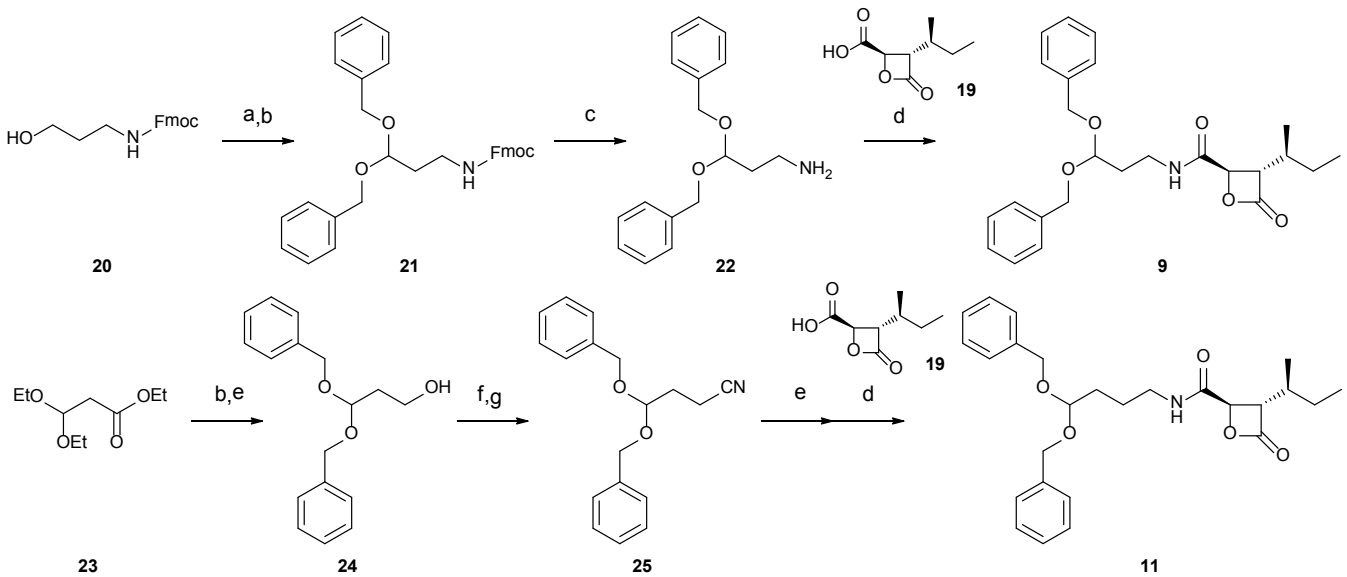
4.6 Hz, 1H, OCOCH), 3.45-3.35 (m, 1H, C<u>H</u>$_2$NH), 3.30-3.21 (m, 1H, C<u>H</u>$_2$NH), 2.85-2.73 (m, 8H, benzyl CH$_2$ and BnCH$_2$), 2.73-2.62 (m, 2H, C<u>H</u>$_2$CH$_2$CH$_2$NH), 2.02-1.92 (m, 1H, *sec*-butyl CH), 1.72-1.60 (m, 3H, C<u>H</u>$_2$CH$_2$NH and *sec*-butyl CH$_2$ (1H)), 1.37-1.24 (m, 1H, *sec*-butyl CH$_2$), 1.07 (d, J = 6.3 Hz, 3H, *sec*-butyl CH$_3$), 0.94 (dd, J = 7.4, 7.4 Hz, 3H, *sec*-butyl CH$_3$); ^{13}C-NMR (125 MHz, CDCl$_3$) δ 169.4, 167.8, 140.2, 128.7, 128.4, 126.1, 70.7, 62.8, 55.7, 53.0, 39.6, 33.8, 33.1, 26.6, 25.4, 16.3, 11.0; LRMS (ESI) *m/z* 437.28 [(M+H)$^+$]; HRMS (ESI) calcd for $C_{27}H_{37}N_2O_3$: 437.2799 [(M+H)$^+$], found: 437.2800.

Target compound **8**

The crude product was purified by silica gel column chromatography (*n*-hexane/ AcOEt 1:2) to yield target compound **8** (47.9 mg, 0.103 mmol, 2 steps 67%) as a colorless oil. $[\alpha]^{25}_D$ -7.17 (*c* 0.51, CH$_2$Cl$_2$); ^{1}H-NMR (500 MHz, CDCl$_3$) δ 8.25 (br, 1H, amide NH), 7.32-7.14 (m, 10H, aromatic), 4.54 (d, J = 4.6 Hz, 1H, NHCOC<u>H</u>), 3.52 (dd, J = 8.0, 4.6 Hz, 1H, OCOCH), 3.48-3.38 (m, 1H, C<u>H</u>$_2$NH), 3.38-3.28 (m, 1H, C<u>H</u>$_2$NH), 2.64-2.39 (m, 10H, benzyl CH$_2$, BnCH$_2$C<u>H</u>$_2$ and C<u>H</u>$_2$CH$_2$CH$_2$NH), 2.02-1.91 (m, 1H, *sec*-butyl CH), 1.77 (tt, J = 8.0, 7.4 Hz, 4H, BnCH$_2$), 1.74-1.54 (m, 3H, C<u>H</u>$_2$CH$_2$NH and *sec*-butyl CH$_2$ (1H)), 1.37-1.21 (m, 1H, *sec*-butyl CH$_2$), 1.07 (d, J = 6.9 Hz, 3H, *sec*-butyl CH$_3$), 0.94 (dd, J = 7.4, 7.4 Hz, 3H, *sec*-butyl CH$_3$); ^{13}C-NMR (125 MHz, CDCl$_3$) δ 169.4, 167.8, 142.0, 128.3, 125.8, 70.8, 62.8, 53.5, 39.9, 33.8, 33.7, 28.1, 26.6, 25.1, 16.3, 11.0; LRMS (ESI) *m/z* 465.31 [(M+H)$^+$]; HRMS (ESI) calcd for $C_{29}H_{41}N_2O_3$: 465.3112 [(M+H)$^+$], found: 465.3115.

Synthetic procedures for 9 and 11

Scheme S2. Synthesis of ether-type (acetal) targets **9** and **11**[a]



[a]Reagents and conditions: (a) Dess-Martin periodinane, CH$_2$Cl$_2$; (b) BnOH, *p*-TsOH, benzene, reflux, 2 steps 57% for **21**; (c) K$_2$CO$_3$, MeOH, 97%; (d) **19**, PivCl, Et$_3$N, CH$_2$Cl$_2$, 0 °C to rt, 95% for **9**, 2 steps quant. for **11**; (e) LiAlH$_4$, Et$_2$O, 0 °C to rt, 2 steps 60% for **24**; (f) MsCl, Et$_3$N, CH$_2$Cl$_2$, 0 °C; (g) NaCN, DMSO, 60 °C, 2 steps 92%.

(9*H*-fluoren-9-yl)methyl (3,3-bis(benzyloxy)propyl)carbamate **21**

To a solution of carbamate **20** (594 mg, 2.00 mmol) in DCM (20 ml) was added DMP (1.27 g, 3.00 mmol, 1.5 equiv). After 30 min at rt, the reaction was quenched with a solution of sat. $Na_2S_2O_3$ and sat. $NaHCO_3$ (1:3), extracted with $CHCl_3$, the organic layer was washed with water, dried over Na_2SO_4 and the solvent was removed under reduced pressure to yield the corresponding aldehyde as a white solid.

To a solution of the solid in benzene (20 ml) was added BnOH (827 µl, 7.99 mmol, 4.0 equiv) and *p*-TsOH·H_2O (3.80 mg, 0.0200 mmol, 0.01 equiv) and the resulting mixture was refluxed in a flask equipped with a Dean-Stark trap. After 19 h, the reaction mixture was concentrated *in vacuo* and the residue was dissolved in $CHCl_3$, washed with sat. $NaHCO_3$, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (*n*-hexane/ AcOEt 15:1-5:1) to yield benzyl acetal **21** (560 mg, 1.13 mmol, 2 steps 57%) as a white solid. mp 93-94 °C; ^{1}H-NMR (400 MHz, $CDCl_3$, 328 K) δ 7.73 (d, *J* = 7.6 Hz, 2H, aromatic), 7.54 (d, *J* = 7.2 Hz, 2H, aromatic), 7.40-7.21 (m, 14H, aromatic), 5.02 (br, 1H, carbamate NH), 4.78 (t, *J* = 4.9 Hz, 1H, OCHO), 4.67 (d, *J* = 11.7 Hz, 2H, benzyl CH_2), 4.56 (d, *J* = 11.7 Hz, 2H, benzyl CH_2), 4.36 (d, *J* = 6.7 Hz, 2H, Fmoc CH_2), 4.17 (t, *J* = 6.7 Hz, 1H, Fmoc CH), 3.31 (br, 2H, C<u>H</u>$_2$NH), 1.94 (br, 2H, C<u>H</u>$_2$CH$_2$NH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.3, 143.9, 141.2, 137.7, 128.5, 127.8, 127.6, 127.0, 125.0, 119.9, 101.0, 67.9, 66.5, 47.2, 37.0, 33.1; LRMS (ESI) *m/z* 516.22 [$(M+Na)^+$]; HRMS (ESI) calcd for $C_{32}H_{31}NO_4Na$: 516.2145 [$(M+Na)^+$], found: 516.2142.

3,3-bis(benzyloxy)propan-1-amine **22**

To a solution of benzyl acetal **21** (117 mg, 0.236 mmol) in MeOH (25 ml) was added K_2CO_3 (326 mg, 2.36 mmol, 10 equiv). After 23 h at rt, the reaction mixture was concentrated *in vacuo*. The crude product was purified by NH-silica gel column chromatography (*n*-hexane/ $CHCl_3$/ MeOH 1:0:0-0:4:1) to yield amine **22** (62.1 mg, 0.229 mmol, 97%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.44-7.25 (m, 10H, aromatic), 4.85 (t, *J* = 5.8 Hz, 1H, OCHO), 4.67 (d, *J* = 11.7 Hz, 2H, benzyl CH_2), 4.58 (d, *J* = 11.7 Hz, 2H, benzyl CH_2), 2.82 (t, *J* = 6.7 Hz, 2H, C<u>H</u>$_2$NH), 1.92 (td, *J* = 6.7, 5.8 Hz, 2H, C<u>H</u>$_2$CH$_2$NH$_2$), 1.44 (br, 2H, NH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 138.1, 128.5, 128.4, 127.9, 127.8, 127.8, 127.7, 127.6, 100.8, 67.4, 38.1, 37.0; LRMS (APCI) *m/z* 272.16 [$(M+H)^+$]; HRMS (APCI) calcd for $C_{17}H_{22}NO_2$: 272.1645 [$(M+H)^+$], found: 272.1648.

Target compound **9**

To a solution of carboxylic acid **19**[1] (54.9 mg, 0.319 mmol, 2.5 equiv) in DCM (3.0 ml) was added triethylamine (44.4 µl, 0.319 mmol, 2.5 equiv) and PivCl (36.1 µl, 0.293 mmol, 2.3 equiv) at 0 °C. After 30 min at 0 °C, the reaction mixture was used as a solution of the corresponding acid anhydride in DCM.

To a solution of amine **22** (34.6 mg, 0.128 mmol, 1.0 equiv) in DCM (1.5 ml) was added triethylamine (26.6 µl, 0.191 mmol, 1.5 equiv) and a solution of the acid anhydride in DCM at 0 °C. After 5 min at 0 °C, the reaction mixture was warmed to rt and stirred for 19 h. The reaction mixture was diluted with AcOEt, washed with 1M HCl, sat. $NaHCO_3$ and brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (*n*-hexane/ AcOEt 3:1) to yield target compound **9** (51.7 mg, 0.122 mmol, 95%) as a colorless oil. $[\alpha]^{23}_D$ 4.44 (*c* 0.94, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.42-7.27 (m, 10H, aromatic), 6.84 (br, 1H, amide NH), 4.80 (dd, *J* = 5.4, 4.9 Hz, 1H, OCHO), 4.70 (d, *J* = 11.7 Hz, 1H, benzyl CH_2), 4.69 (d, *J* = 11.7 Hz, 1H, benzyl CH_2), 4.57 (d, *J* = 11.7 Hz, 1H, benzyl CH_2), 4.56 (d, *J* = 11.7 Hz, 1H, benzyl CH_2), 4.51 (d, *J* = 4.5 Hz, 1H, NHCOC<u>H</u>), 3.53 (dd, *J* = 7.6, 4.5 Hz, 1H, OCOCH), 3.53-3.34 (m, 2H, C<u>H</u>$_2$NH), 2.03-1.88 (m, 3H, C<u>H</u>$_2$CH$_2$NH

and *sec*-butyl CH), 1.72-1.58 (m, 1H, *sec*-butyl CH_2), 1.38-1.21 (m, 1H, *sec*-butyl CH_2), 1.05 (d, J = 6.7 Hz, 3H, *sec*-butyl CH_3), 0.94 (dd, J = 7.6, 7.2 Hz, 3H, *sec*-butyl CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.1, 167.7, 137.5, 128.6, 127.9, 127.9, 100.9, 70.6, 68.3, 68.2, 62.8, 35.0, 33.8, 32.6, 26.6, 16.3, 11.0; LRMS (ESI) *m/z* 448.21 [$(M+Na)^+$]; HRMS (ESI) calcd for $C_{25}H_{31}NO_5Na$: 448.2094 [$(M+Na)^+$], found: 448.2098.

3,3-bis(benzyloxy)propan-1-ol **24**

To a solution of ethyl 3,3-diethoxypropanoate **23** (118 µl, 0.607 mmol) in benzene (10 ml) was added BnOH (251 µl, 2.43 mmol, 4.0 equiv) and *p*-TsOH·H_2O (1.15 mg, 0.00607 mmol, 0.01 equiv). The reaction mixture was refluxed in a flask equipped with a Dean-Stark trap for 30 h. The reaction mixture was diluted with AcOEt, washed with sat. $NaHCO_3$ and brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (*n*-hexane/ AcOEt 10:1) to give the corresponding benzyl acetal as a colorless liquid.

To a solution of $LiAlH_4$ (69.1 mg, 1.82 mmol, 3.0 equiv) in Et_2O (2.0 ml) was added the aforementioned liquid in Et_2O (1.0 ml) *via cannula* at 0 °C. After 5 min at 0 °C, the reaction mixture was warmed to rt and stirred for 2 h. To the reaction mixture was added water (69.1 µl), 15% NaOH (69.1 µl) and water (207 µl) at 0 °C and the resulting mixture was vigorously stirred at rt for 1 h. The mixture was filtered through a Celite pad and the filtrate was concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (*n*-hexane/ AcOEt 3:1) to yield alcohol **24** (99.2 mg, 0.364 mmol, 2 steps 60%) as a colorless liquid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.40-7.26 (m, 10H, aromatic), 4.92 (t, J = 5.4 Hz, 1H, OCHO), 4.71 (d, J = 11.8 Hz, 2H, benzyl CH_2), 4.59 (d, J = 11.8 Hz, 2H, benzyl CH_2), 3.75 (t, J = 5.4 Hz, 2H, $C\underline{H}_2OH$), 2.36 (br, 1H, OH), 2.01 (td, J = 5.4, 5.4 Hz, 2H, $C\underline{H}_2CH_2OH$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 137.7, 128.5, 127.8, 101.4, 68.0, 59.0, 35.6; LRMS (ESI) *m/z* 295.13 [$(M+Na)^+$]; HRMS (ESI) calcd for $C_{17}H_{20}O_3Na$: 295.1305 [$(M+Na)^+$], found: 295.1305. ^{1}H-NMR and ^{13}C-NMR are in agreement with that reported by Colson.[2]

4,4-bis(benzyloxy)butanenitrile **25**

To a solution of alcohol **24** (99.2 mg, 0.364 mmol) in DCM (5.0 ml) was added triethylamine (76.1 µl, 0.547 mmol, 1.5 equiv) and MsCl (33.8 µl, 0.437 mmol, 1.2 equiv) at 0 °C. After 30 min at 0 °C, the reaction mixture was diluted with AcOEt, washed with water and brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure to give the corresponding mesylated product as a colorless oil.

To a solution of the oil in DMSO (410 µl) was added NaCN (107 mg, 2.19 mmol, 6.0 equiv). After 15 h at 60 °C, the reaction mixture was diluted with AcOEt, washed with water and brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (*n*-hexane/ AcOEt 10:1) to yield nitrile **25** (97.1 mg, 0.345 mmol, 2 steps 95%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.41-7.26 (m, 10H, aromatic), 4.81 (t, J = 5.4 Hz, 1H, OCHO), 4.69 (d, J = 11.7 Hz, 2H, benzyl CH_2), 4.56 (d, J = 11.7 Hz, 2H, benzyl CH_2), 2.42 (t, J = 7.2 Hz, 2H, CH_2CN), 2.04 (m, 2H, $C\underline{H}_2CH_2CN$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 137.4, 128.5, 127.9, 127.8, 119.3, 100.0, 68.4, 29.4, 12.4; LRMS (ESI) *m/z* 304.13 [$(M+Na)^+$]; HRMS (ESI) calcd for $C_{18}H_{19}NO_2Na$: 304.1308 [$(M+Na)^+$], found: 304.1307.

Target compound **11**

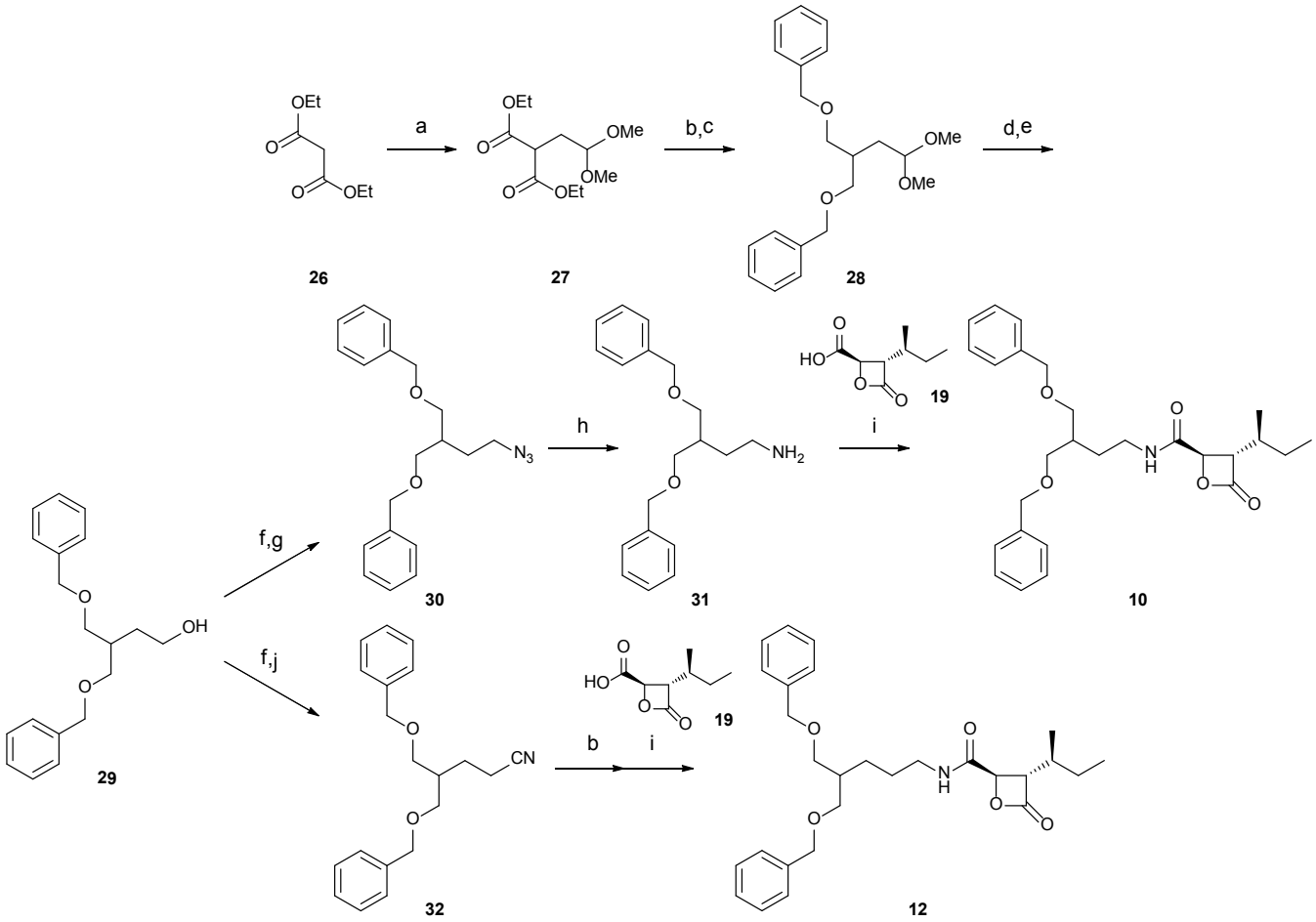
To a solution of nitrile **25** (28.7 mg, 0.102 mmol) in Et_2O (1.0 ml) was added $LiAlH_4$ (15.5 mg, 0.408 mmol, 4.0 equiv) at 0 °C. After 5 min at 0 °C, the reaction mixture was warmed to rt and stirred for 12 h. To the reaction mixture was added water (28.7 µl), 15% NaOH (28.7 µl) and water (86.1 µl) at 0 °C and the resulting mixture was vigorously stirred at rt for 1 h. The mixture was filtered through a Celite pad and the filtrate was concentrated *in vacuo* to give the corresponding amine as a colorless oil.

To a solution of carboxylic acid **19**[1] (43.9 mg, 0.255 mmol, 2.5 equiv) in DCM (2.5 ml) was added triethylamine (35.5 µl, 0.255 mmol, 2.5 equiv) and PivCl (28.3 µl, 0.230 mmol, 2.3 equiv) at 0 °C. After 30 min at 0 °C, the reaction mixture was used as a solution of the corresponding acid anhydride in DCM.

To a solution of the aforementioned amine in DCM (1.0 ml) was added triethylamine (21.4 µl, 0.154 mmol, 1.5 equiv) and a solution of the acid anhydride in DCM at 0 °C. After 5 min at 0 °C, the reaction mixture was warmed to rt and stirred for 19 h. The reaction mixture was diluted with AcOEt, washed with 1 M HCl, sat. $NaHCO_3$ and brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (*n*-hexane/ AcOEt 3:1) to yield target compound **11** (45.9 mg, 0.104 mmol, 2 steps quant.) as a colorless oil. $[\alpha]^{24}_D$ 12.22 (*c* 0.62, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.40-7.27 (m, 10H, aromatic), 6.52 (br, 1H, amide NH), 4.74 (t, *J* = 5.7 Hz, 1H, OCHO), 4.68 (d, *J* = 11.5 Hz, 1H, benzyl CH_2), 4.67 (d, *J* = 11.5 Hz, 1H, benzyl CH_2), 4.57 (d, *J* = 4.6 Hz, 1H, NHCOC<u>H</u>), 4.56 (d, *J* = 11.5 Hz, 2H, benzyl CH_2), 3.55 (dd, *J* = 7.4, 4.6 Hz, 1H, OCOCH), 3.39-3.24 (m, 2H, C<u>H</u>$_2$NH), 2.03-1.92 (m, 1H, *sec*-butyl CH), 1.82-1.73 (m, 2H, C<u>H</u>$_2$CH$_2$CH$_2$NH), 1.71-1.59 (m, 3H, C<u>H</u>$_2$CH$_2$NH and *sec*-butyl CH_2 (1H)), 1.37-1.25 (m, 1H, *sec*-butyl CH_2), 1.07 (d, *J* = 6.9 Hz, 3H, *sec*-butyl CH_3), 0.94 (dd, *J* = 7.4, 7.4 Hz, 3H, *sec*-butyl CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 169.2, 167.8, 137.9, 128.5, 127.8, 127.8, 127.7, 101.5, 70.7, 67.7, 67.7, 62.9, 38.9, 33.8, 30.7, 26.6, 24.3, 16.3, 11.0; LRMS (ESI) *m/z* 462.23 [$(M+Na)^+$]; HRMS (ESI) calcd for $C_{26}H_{33}NO_5Na$: 462.2251 [$(M+Na)^+$], found: 462.2253.

Synthetic procedures for 10 and 12

Scheme S3. Synthesis of ether-type targets **10** and **12**[a]



[a]Reagents and conditions: (a) bromoacetaldehyde diethyl acetal, NaOEt, EtOH, rt to reflux, 59% (b) $LiAlH_4$, Et_2O, 0 °C to rt; (c) NaH, BnBr, DMF, 0 °C, to rt, 2 steps 64%; (d) AcOH, H_2O; (e) $NaBH_4$, MeOH, 0 °C to rt, 2 steps 97%; (f) MsCl, Et_3N, CH_2Cl_2, 0 °C; (g) NaN_3, DMF, 70 °C, 2 steps 91%; (h) PPh_3, H_2O/THF, rt to reflux, quant.; (i) **19**, PivCl, Et_3N, CH_2Cl_2, 0 °C to rt, quant. for **10**, 2 steps quant. for **12**; (j) NaCN, DMSO, 60 °C, 2 steps 98%.

diethyl 2-(2,2-dimethoxyethyl)malonate **27**

To a solution of sodium ethoxide (9.06 g, 133 mmol, 1.1 equiv) in EtOH (90 ml) was added diethyl malonate (18.3 ml, 121 mmol, 1.0 equiv). After 1 h at rt, bromoacetaldehyde dimethyl acetal (19.9 ml, 169 mmol, 1.4 equiv) was added and the resulting mixture was refluxed for 23 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in DCM, washed with water, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (*n*-hexane/ AcOEt 20:1) to yield compound **27** (17.8 g, 71.7 mmol, 59%) as a colorless liquid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.43 (t, J = 5.8 Hz, 1H, OCHO), 4.21 (q, J = 7.2 Hz, 2H, OCH_2), 4.20 (q, J = 7.2 Hz, 2H, OCH_2), 3.49 (t, J = 7.2 Hz, 1H, COCHCO), 3.33 (s, 6H, OCH_3), 2.22 (dd, J = 7.2, 5.8 Hz, 2H, $CHCH_2CH$), 1.27 (t, J = 7.2 Hz, 6H, OCH_2CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.2, 102.5, 61.4, 53.4, 47.8, 31.7, 14.0; LRMS (ESI) *m/z* 271.11 [$(M+Na)^+$]; HRMS (ESI) calcd for $C_{11}H_{20}O_6Na$: 271.1152 [$(M+Na)^+$], found: 271.1152. ^{1}H-NMR and ^{13}C-NMR are in agreement with that reported by Vignola.[3]

(((2-(2,2-dimethoxyethyl)propane-1,3-diyl)bis(oxy))bis(methylene))dibenzene **28**

To a solution of $LiAlH_4$ (3.64 g, 96.0 mmol, 3.0 equiv) in Et_2O (100 ml) was added compound **27** (7.94 g, 32.0 mmol) in Et_2O (45 ml) *via cannula* at 0 °C. After 5 min at 0 °C, the reaction mixture was warmed to rt and stirred for 2 h. To the reaction mixture was added water (3.64 ml), 15% NaOH (3.64 ml) and water (10.9 ml) at 0 °C, and the resulting mixture was vigorously stirred at rt for 1 h. The mixture was filtered through a Celite pad and the filtrate was concentrated *in vacuo* to give the corresponding diol as a colorless liquid.

To a solution of the liquid in DMF (40 ml) was added NaH (3.84 g, 95.9 mmol, 3.0 equiv, 60% oil suspension) at 0 °C. After 30 min at 0 °C, BnBr (9.49 ml, 79.9 mmol, 2.5 equiv) was added and the resulting mixture was warmed to rt. After 35 h at rt, the reaction was quenched with sat. NH_4Cl (70 ml) at 0 °C. The resulting mixture was extracted with AcOEt and the organic layer was washed with water and brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (*n*-hexane/ AcOEt 10:1) to yield compound **28** (7.00 g, 20.3 mmol, 2 steps 64%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.38-7.22 (m, 10H, aromatic), 4.49 (s, 4H, benzyl CH_2), 4.49 (t, J = 6.3 Hz, 1H, OCHO), 3.55-3.45 (m, 4H, $OC\underline{H}_2CH$), 3.28 (s, 6H, OCH_3), 2.15-2.03 (m, 1H, $CH_2C\underline{H}CH_2$), 1.71 (dd, J = 6.3, 6.3 Hz, 2H, $CHC\underline{H}_2CH$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 138.6, 128.3, 127.5, 127.4, 103.1, 73.0, 70.8, 52.6, 35.6, 31.6; LRMS (ESI) *m/z* 367.19 [$(M+Na)^+$]; HRMS (ESI) calcd for $C_{21}H_{28}O_4Na$: 367.1880 [$(M+Na)^+$], found: 367.1877.

4-(benzyloxy)-3-((benzyloxy)methyl)butan-1-ol **29**

To an emulsion of compound **28** (2.02 g, 5.87 mmol) in water (6.0 ml) was added acetic acid (6.0 ml). The resulting mixture was vigorously stirred for 5 h. The reaction mixture was diluted with AcOEt, washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure to give the corresponding aldehyde as a colorless oil.

To a solution of the oil in MeOH (60 ml) was added $NaBH_4$ (111 mg, 2.94 mmol, 0.5 equiv) at 0 °C. After 5 min at 0 °C, the reaction mixture was warmed to rt. After 4 min at rt, acetone (60 ml) was added. After 1 h at rt, the resulting mixture was concentrated *in vacuo*. The residue was dissolved in AcOEt, washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (*n*-hexane/ AcOEt 4:1) to yield alcohol **29** (1.71 g, 5.70 mmol, 2 steps 97%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.38-7.25 (m, 10H, aromatic), 4.50 (s, 4H, benzyl CH_2), 3.66 (t, J = 6.3 Hz, 2H, $C\underline{H}_2OH$), 3.53 (dd, J = 9.0, 6.3 Hz, 2H, $OC\underline{H}_2CH$), 3.44 (dd, J = 9.0, 5.8 Hz, 2H, $OC\underline{H}_2CH$), 3.01 (s, 1H, OH), 2.13 (ttt, J = 6.3, 6.3, 5.8 Hz, 1H, $CH_2C\underline{H}CH_2$), 1.67 (td, J = 6.3, 6.3 Hz, 2H, $C\underline{H}_2CH_2OH$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 138.0, 128.4, 127.6, 73.2, 71.7, 61.0, 37.7, 33.6; LRMS (ESI) *m/z* 323.16 [$(M+Na)^+$]; HRMS (ESI) calcd for $C_{19}H_{24}O_3Na$: 323.1618 [$(M+Na)^+$], found: 323.1616.

(((2-(2-azidoethyl)propane-1,3-diyl)bis(oxy))bis(methylene))dibenzene **30**

To a solution of alcohol **29** (224 mg, 0.746 mmol) in DCM (3.0 ml) was added triethylamine (156 µl, 1.12 mmol, 1.5 equiv) and MsCl (69.3 µl, 0.895 mmol, 1.2 equiv) at 0 °C. After 30 min at 0 °C, the reaction mixture was diluted with AcOEt, washed with water and brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure to give the corresponding mesylated product as a colorless oil.

To a solution of the oil in DMF (2.5 ml) was added NaN_3 (146 mg, 2.24 mmol, 3.0 equiv). After 3 h at 70 °C, the reaction mixture was diluted with AcOEt, washed with water and brine, dried over Na_2SO_4 and the solvent was

removed under reduced pressure. The crude product was purified by silica gel column chromatography (*n*-hexane/ AcOEt 15:1) to yield azide **30** (223 mg, 0.685 mmol, 2 steps 91%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.37-7.24 (m, 10H, aromatic), 4.48 (s, 4H, benzyl CH_2), 3.50 (dd, J = 9.4, 5.4 Hz, 2H, OC$\underline{H}_2$CH), 3.46 (dd, J = 9.4, 5.4 Hz, 2H, OC$\underline{H}_2$CH), 3.32 (t, J = 7.2 Hz, 2H, C$\underline{H}_2$N$_3$), 2.05 (m, 1H, $CH_2C\underline{H}CH_2$), 1.71 (td, J = 7.2, 7.2 Hz, 2H, C$\underline{H}_2CH_2N_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 138.3, 128.3, 127.5, 73.1, 70.5, 49.5, 37.0, 28.3; LRMS (ESI) *m/z* 348.17 [$(M+Na)^+$]; HRMS (ESI) calcd for $C_{19}H_{23}N_3O_2Na$: 348.1683 [$(M+Na)^+$], found: 348.1681.

4-(benzyloxy)-3-((benzyloxy)methyl)butan-1-amine **31**

To a solution of azide **30** (71.1 mg, 0.219 mmol) in THF (2.2 ml) was added PPh_3 (63.0 mg, 0.240 mmol, 1.1 equiv) and water (220 µl). After 9 h at rt, the reaction mixture was refluxed for 22 h. The resulting mixture was concentrated *in vacuo* and the crude product was purified by silica gel column chromatography (*n*-hexane/ AcOEt/ $CHCl_3$/ MeOH 1:2:0:0-0:0:1:1-0:0:0:1) to yield amine **31** (68.5 mg, 0.229 mmol, quant.) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.37-7.23 (m, 10H, aromatic), 4.48 (s, 4H, benzyl CH_2), 3.50 (dd, J = 9.4, 5.8 Hz, 2H, OC$\underline{H}_2$CH), 3.45 (dd, J = 9.4, 5.8 Hz, 2H, OC$\underline{H}_2$CH), 2.74 (t, J = 7.2 Hz, 2H, C$\underline{H}_2NH_2$), 2.09-1.92 (m, 1H, $CH_2C\underline{H}CH_2$), 1.99 (br, 2H, NH_2), 1.56 (td, J = 7.2, 7.2 Hz, 2H, C$\underline{H}_2CH_2NH_2$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 138.5, 128.3, 127.5, 127.5, 73.1, 71.0, 39.9, 37.3, 33.0; LRMS (ESI) *m/z* 300.20 [$(M+H)^+$]; HRMS (ESI) calcd for $C_{19}H_{26}NO_2$: 300.1958 [$(M+H)^+$], found: 300.1957.

Target compound **10**

To a solution of carboxylic acid **19**[1] (46.1 mg, 0.268 mmol, 2.5 equiv) in DCM (3.0 ml) was added triethylamine (37.3 µl, 0.268 mmol, 1.0 equiv) and PivCl (29.7 µl, 0.241 mmol, 2.3 equiv) at 0 °C. After 30 min at 0 °C, the reaction mixture was used as a solution of the corresponding acid anhydride in DCM.

To a solution of amine **31** (32.1 mg, 0.107 mmol, 1.0 equiv) in DCM (1.5 ml) was added triethylamine (22.4 µl, 0.161 mmol, 1.5 equiv) and a solution of the acid anhydride in DCM at 0 °C. After 5 min at 0 °C, the reaction mixture was warmed to rt and stirred for 19 h. The reaction mixture was diluted with AcOEt, washed with 1M HCl, sat. $NaHCO_3$ and brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (*n*-hexane/ AcOEt 3:1) to yield target compound **10** (50.3 mg, 0.111 mmol, quant.) as a colorless oil. $[\alpha]^{24}_D$ 9.28 (*c* 0.74, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.38-7.24 (m, 10H, aromatic), 6.95 (br, 1H, amide NH), 4.53 (d, J = 4.6 Hz, 1H, NHCOC$\underline{H}$), 4.49 (s, 4H, benzyl CH_2), 3.56 (dd, J = 7.4, 4.6 Hz, 1H, OCOCH), 3.52-3.46 (m, 2H, OC$\underline{H}_2$CH), 3.45-3.29 (m, 4H, OC$\underline{H}_2$CH and C$\underline{H}_2$NH), 2.03-1.91 (m, 2H, $CH_2C\underline{H}CH_2$ and *sec*-butyl CH), 1.72-1.61 (m, 3H, C$\underline{H}_2CH_2$NH and *sec*-butyl CH_2 (1H)), 1.36-1.24 (m, 1H, *sec*-butyl CH_2), 1.06 (d, J = 6.9 Hz, 3H, *sec*-butyl CH_3), 0.94 (dd, J = 7.4, 7.4 Hz, 3H, *sec*-butyl CH_3); ^{13}C-NMR (125 MHz, $CHCl_3$) δ 169.3, 167.8, 138.1, 128.4, 128.4, 127.7, 127.6, 127.6, 73.2, 71.1, 71.0, 70.7, 62.8, 37.8, 37.6, 33.8, 29.1, 26.6, 16.3, 11.0; LRMS (ESI) *m/z* 454.26 [$(M+H)^+$]; HRMS (ESI) calcd for $C_{27}H_{36}NO_5$: 454.2588 [$(M+H)^+$], found: 454.2595.

5-(benzyloxy)-4-((benzyloxy)methyl)pentanenitrile **32**

To a solution of alcohol **29** (279 mg, 0.929 mmol) in DCM (3.7 ml) was added triethylamine (193 µl, 1.39 mmol, 1.5 equiv) and MsCl (86.3 µl, 1.11 mmol, 1.2 equiv) at 0 °C. After 30 min at 0 °C, the reaction mixture was diluted with AcOEt, washed with water and brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure to give

the corresponding mesylated product as a colorless oil.

To a solution of the oil in DMSO (1.0 ml) was added NaCN (273 mg, 5.57 mmol, 6.0 equiv). After 3 h at 60 °C, the reaction mixture was diluted with AcOEt, washed with water and brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (*n*-hexane/ AcOEt 7:1) to yield nitrile **32** (282 mg, 0.910 mmol, 2 steps 98%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.38-7.25 (m, 10H, aromatic), 4.47 (s, 4H, benzyl CH_2), 3.50 (dd, J = 9.4, 5.8 Hz, 2H, OCH_2CH), 3.45 (dd, J = 9.4, 5.4 Hz, 2H, OCH_2CH), 2.38 (t, J = 7.2 Hz, 2H, CH_2CN), 2.06 (m, 1H, CH_2CHCH_2), 1.80 (td, J = 7.2, 7.2 Hz, 2H, CH_2CH_2CN); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 138.1, 128.4, 127.6, 127.5, 119.9, 73.1, 70.2, 38.4, 25.2, 15.1; LRMS (ESI) *m/z* 332.16 [$(M+Na)^+$]; HRMS (ESI) calcd for $C_{20}H_{23}NO_2Na$: 332.1620 [$(M+Na)^+$], found: 332.1620.

Target compound **12**

To a solution of $LiAlH_4$ (20.7 mg, 0.546 mmol, 4.4 equiv) in Et_2O (1.0 ml) was added nitrile **32** (38.4 mg, 0.124 mmol) in Et_2O (1.0 ml) *via cannula* at 0 °C. After 5 min at 0 °C, the reaction mixture was warmed to rt and stirred for 5 h. To the reaction mixture was added water (20.7 µl), 15% NaOH (20.7 µl) and water (62.1 µl) at 0 °C and the resulting mixture was vigorously stirred at rt for 1 h. The mixture was filtered through a Celite pad and the filtrate was concentrated *in vacuo* to give the corresponding amine as a colorless oil.

To a solution of carboxylic acid **19**[1] (53.4 mg, 0.310 mmol, 2.5 equiv) in DCM (3.0 ml) was added triethylamine (43.1 µl, 0.310 mmol, 2.5 equiv) and PivCl (34.4 µl, 0.279 mmol, 2.3 equiv) at 0 °C. After 30 min at 0 °C, the reaction mixture was used as a solution of the corresponding acid anhydride in DCM.

To a solution of the aforementioned amine in DCM (1.2 ml) was added triethylamine (25.9 µl, 0.186 mmol, 1.5 equiv) and a solution of the acid anhydride in DCM at 0 °C. After 5 min at 0 °C, the reaction mixture was warmed to rt and stirred for 19 h. The reaction mixture was diluted with AcOEt, washed with 1 M HCl, sat. $NaHCO_3$ and brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (*n*-hexane/ AcOEt 3:1) to yield target compound **12** (58.5 mg, 0.125 mmol, 2 steps quant.) as a colorless oil. $[\alpha]^{24}_D$ 13.20 (*c* 1.05, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.37-7.25 (m, 10H, aromatic), 6.41 (br, 1H, amide NH), 4.56 (d, J = 4.6 Hz, 1H, NHCOCH), 4.48 (s, 4H, benzyl CH_2), 3.56 (dd, J = 8.0, 4.6 Hz, 1H, OCOCH), 3.49 (dd, J = 9.2, 5.7 Hz, 2H, OCH_2CH), 3.44 (dd, J = 9.2, 5.7 Hz, 2H, OCH_2CH), 3.37-3.20 (m, 2H, CH_2NH), 2.02-1.88 (m, 2H, NHCOCH and CH_2CHCH_2), 1.71-1.61 (m, 1H, *sec*-butyl CH), 1.59-1.50 (m, 2H, CH_2CH_2NH), 1.47-1.39 (m, 2H, $CH_2CH_2CH_2NH$), 1.37-1.26 (m, 1H, *sec*-butyl CH_2), 1.07 (d, J = 6.3 Hz, 3H, *sec*-butyl CH_3), 0.94 (dd, J = 7.4, 7.4 Hz, 3H, *sec*-butyl CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 169.2, 167.8, 138.5, 128.3, 127.6, 127.5, 73.1, 70.7, 62.9, 39.4, 39.0, 33.8, 26.8, 26.6, 25.9, 16.3, 11.0; LRMS (ESI) *m/z* 468.28 [$(M+H)^+$]; HRMS (ESI) calcd for $C_{28}H_{38}NO_5$: 468.2745 [$(M+H)^+$], found: 468.2754.

Flexible alignment of compounds 5-12

Flexible alignment of compounds **5-12** onto previously analyzed non-covalent binding conformation of compound **4**[4] and covalent binding conformation of homobelactosin C derivatives analyzed by Meijere *et al.*[5, 6] was performed by using Molecular Operating Environment (MOE) 2012.10. Prior to the calculation, β-lactone ring of compounds **5-12** was superimposed with that of **4** and the position was fixed during the calculation. Default values were used for all parameters and the top ranked pose of each compounds were shown in this paper.

Proteasomes assay

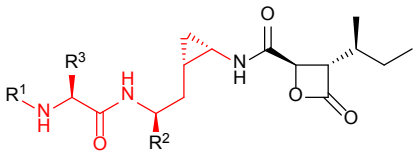
Inhibitory activity of the target compounds **5-12** on ChT-L activity of the human 20S proteasome was measured as described previously.[7]

Cell proliferation assay

Inhibitory activity of the target compounds **5-12** on HCT116 cell growth was measured as described previously.[7]

BEI and SEI values of analogs of 4 with same scaffold

Table S1. BEI and SEI values of analogs of **4** with same scaffold



compound number	R^1	R^2	R^3	BEI	SEI
S1	Cbz	vinyl	Me	35	14
S2	H	vinyl	Me	43	14
S3	Cbz	vinyl	epi-Me	34	14
S4	Cbz	vinyl	H	36	14
S5	Cbz	vinyl	isobutyl	32	14
S6	Cbz	vinyl	Bn	31	14
S7	Cbz	vinyl	3-indolylmethyl	29	13
S8	Ac	vinyl	Me	39	13
S9	Bz	vinyl	Me	36	14
S10	2-naphthoyl	vinyl	Me	35	15
S11	Boc	vinyl	Me	36	13
S12	Cbz	Et	Me	35	14
S13	Cbz	Ph	Me	30	13
S14	Cbz	Bn	Me	33	15
S15	Cbz	phenylpropyl	Me	30	14
S16	Cbz	1-naphthylmethyl	Me	26	13
S17	Cbz	2-naphthylmethyl	Me	26	13
S18	Cbz	1-naphthylethyl	Me	27	13
S19	Cbz	2-naphthylethyl	Me	28	14
S20	2-naphthoyl	phenethyl	Me	32	16

Combustion analysis data for the target compounds

Table S2. Table listing combustion analysis data for the target compounds.

5	Anal. calcd for $C_{26}H_{34}N_2O_3$: C, 73.90; H, 8.11; N, 6.63.	Found: C, 73.71; H, 8.21; N, 6.64.
6	Anal. calcd for $C_{28}H_{38}N_2O_3$: C, 74.63; H, 8.50; N, 6.22.	Found: C, 74.34; H, 8.61; N, 6.15.
7	Anal. calcd for $C_{27}H_{36}N_2O_3 \cdot 0.1H_2O$: C, 73.97; H, 8.32; N, 6.39.	Found: C, 73.80; H, 8.44; N, 6.29.
8	Anal. calcd for $C_{29}H_{40}N_2O_3 \cdot 0.2H_2O$: C, 74.39; H, 8.70; N, 5.98.	Found: C, 74.38; H, 8.77; N, 5.91.
9	Anal. calcd for $C_{25}H_{31}NO_5$: C, 70.57; H, 7.34; N, 3.29.	Found: C, 70.37; H, 7.41; N, 3.32.
10	Anal. calcd for $C_{27}H_{35}NO_5$: C, 71.50; H, 7.78; N, 3.09.	Found: C, 71.26; H, 7.86; N, 3.11.
11	Anal. calcd for $C_{26}H_{33}NO_5$: C, 71.05; H, 7.57; N, 3.19.	Found: C, 70.86; H, 7.61; N, 3.19.
12	Anal. calcd for $C_{28}H_{37}NO_5$: C, 71.92; H, 7.98; N, 3.00.	Found: C, 71.66; H, 7.94; N, 3.06.

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