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# New Inhibitors of the Malaria Aspartyl Proteases Plasmepsin I and II

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**Abstract**—New inhibitors of plasmepsin I and II, the aspartic proteases of the malaria parasite *Plasmodium falciparum*, are described. From paralell solution phase chemistry, several reversed-statine type isostere inhibitors, many of which are aza-peptides, have been prepared. The synthetic strategy delivers the target compounds in good to high overall yields and with excellent stereochemical control throughout the developed route. The final products were tested for their plasmepsin I and II inhibiting properties and were found to exhibit modest but promising activity. The best inhibitor exhibits $K_i$ values of 250 nM and 1.4 μM for Plm I and II, respectively.


## Introduction

Malaria is considered as one of the most serious infectious diseases in the world, affecting approximately 500 million people yearly. It is estimated that the annual mortality from malaria is 2 million people, and that more than 40% of the world's population is at risk of infection.[1] The disease is spread by the *Anopheles* mosquito, mostly found in the tropical regions of the world, although not all species of the mosquito transmit malaria.[2] There are four major species of the malaria parasite, that is *Plasmodium falciparum*, *P. vivax*, *P. malariae*, and *P. ovale*, of which *P. falciparum* is responsible for more than 95% of malaria-related morbidity and mortality.[3] The malaria parasite degrades hemoglobin as a source of nutrients in the erythrocytic stage, where it invades the host red blood cells.[4] The hemoglobin degradation occurs in an acidic food vacuole formed by the parasite, and can result in up to 70% of host hemoglobin being consumed.[1b] The food vacuole contains aspartic, cysteine, and metallo proteases, which are all considered to play a role in the process of hemoglobin degradation.[1b,5,6] Today at least 10 aspartic protease genes have been identified in the *P. falciparum* genome, potentially complicating the picture of target selection and target redundancy.[7] Up until now, only the parasitic cysteine proteases falcipain 1–3 and the aspartic proteases plasmepsin I and II (Plm I and II) have been studied in detail, and inhibitors of falcipains and plasmepsins have shown efficacy in cell and animal models of malaria, suggesting that these enzymes may be suitable molecular tagets for drug discovery.[5a,8]

Previous studies have shown that the hydroxyethylamine core **I**, and the statine derived core **II** (Fig. 1) found in the naturally occurring peptide aspartic protease inhibitor pepstatin A, can function as useful templates for the development of potent plasmepsin inhibitors.[9,10] We have recently reported on the novel reversed-statine type isosteres (*R*,*R*)-**III** and (*S*,*S*)-**III** (Fig. 1), where replacement of the N-terminus of the hydroxyethylamine core **I** with a C-terminus isostere was investigated. These compounds were shown to exhibit modest but promising activity against Plm I and II.[11]

We now report on further refinement and extensions of these inhibitors, resulting in the isosteres (*R*,*R*)-**IV** and

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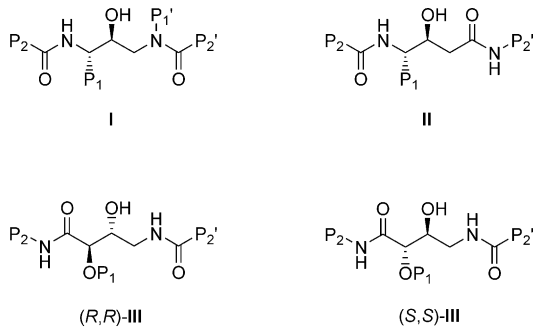



**Figure 1.** The structures of the hydroxyethylamine core (**I**) and the statine-derived core (**II**). (*R*,*R*)-**III** and (*S*,*S*)-**III** are reversed-statine based Plm inhibitors.

(*R*,*R*)-**V** (Fig. 2). To increase affinity to Plm I and II, a benzyl substituent designed to interact with the S1′ pocket of the plasmepsins was appended to the amino terminus nitrogen [cf. isosteres (*R*,*R*)-**III** and (*S*,*S*)-**III**]. To further explore this site of the Plm inhibitor structures, a hydrazine functionality was introduced, providing the *N*-benzyl substituent with increased directional flexibility to fit into the S1′ pocket. This approach has previously successfully been applied in the development of potent and orally bioavailable HIV-1 protease inhibitors.[12]

An efficient synthesis for both classes of compounds has been developed, starting from carbohydrate-derived precursors and resulting in well-optimized high yield reactions. Furthermore, the influence of chirality on inhibitor activity has been determined from synthesis and comparison of the four stereoisomers (regarding the central core) of the promising aza-based inhibitor **32**, which exhibits an inhibition of 68 and 35% for Plm I and II, respectively, at 5 μM.

Of the two sets of compounds synthesized, that is the *N*-benzyl- and the aza-benzyl core compounds, the *N*-benzyl derivatives were essentially inactive whereas the aza-benzyl derivatives exhibited promising activity towards both Plm I and II, for example **32** and **33** (Table 1). From synthesis and evaluation of the stereoisomers of the aza-benzyl inhibitor **32**, substantial potency enhancements were seen with lead inhibitor **57** (*R*,*S* stereochemistry) exhibiting $K_i$ values of 250 nM and 1.4 μM for Plm I and II, respectively (Table 2).

## Results and Discussion

### Chemistry

The synthetic route to compounds of the general structure (*R*,*R*)-**IV** and (*R*,*R*)-**V** (Fig. 2) commenced by

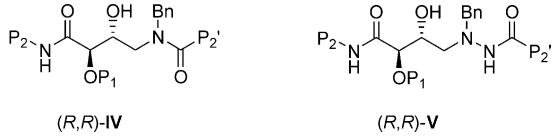



**Figure 2.** The reversed-statine based inhibitors presented in this report.

synthesis of the four epoxides **6**–**9** (Scheme 1). An *R*,*R* configuration of the central core was selected based on previous results.[11] The *p*-bromobenzylated methyl ester **1**[11,13] (*R*,*R*) was hydrolyzed with LiOH in dioxane/$H_2O$ at 0 °C, and then coupled with a selected set of amines,[9,14] using standard coupling conditions, that is *N*′ - (3 - dimethylaminopropyl) - *N* - ethylcarbodiimide hydrochloride (EDC), 1-hydroxybenzotriazole (HOBt), and $Et_3N$ in DMF, to deliver the amides **2**–**5** in 81–93% overall yields. Deprotection of the isopropylidene group in compounds **2**–**5** was achieved using Dowex $H^+$ in MeOH for amides with non-basic side chains, and *p*-TsOH in MeOH for amides with basic side chains. Finally, the epoxides were formed using Mitsunobu conditions, that is $Ph_3P$ and diethylazodicarboxylate (DEAD) in refluxing $CHCl_3$,[15] to provide the epoxides **6**–**9** in 70–89% yield over two steps (Scheme 1).

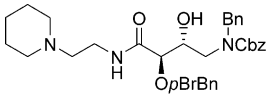
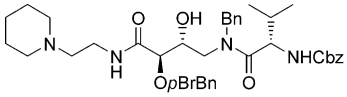
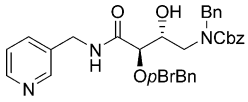
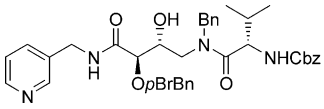
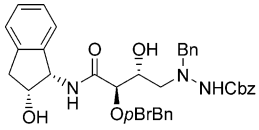
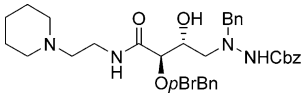
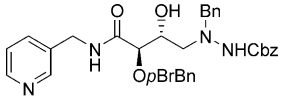
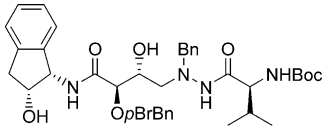
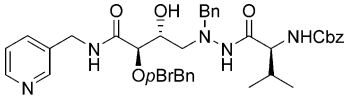
The epoxides **6**–**9** were opened with $BnNH_2$ in MeOH at 50 C[16] to afford the secondary amine target compounds **10**–**13** in 82–93% yield (Scheme 2). Only one regioisomer was observed in each case according to NMR analysis. Subsequently, **10**–**13** were reacted with both di-*tert*-butyl dicarbonate ($Boc_2O$) and benzyl chloroformate (Z-Cl) in $CH_2Cl_2$ containing $Et_3N$ to give the target carbamates **14**, **18**, **22**, **26** and **15**, **19**, **23**, **27** in 86–99% yield, and with Boc-Val or Cbz-Val using *O*-(7-azabenzotriazol - 1 - yl) - *N*,*N*,*N*′,*N*′ - tetramethyluronium-hexafluorophosphate (HATU) and *N*,*N*-diisopropylethylamine (DIEA) in DMF to give the target tertiary amides **16**, **20**, **24**, **28** and **17**, **21**, **25**, **29** in 93–97% yield (Scheme 2).

In order to investigate the combined effect of increased directional flexibility of the *N*-benzyl side chain and the effect of elongation of the core, the *N*-benzyl hydrazines **30**–**45** were prepared (Scheme 3). Hydrazines CbzNHNHBn and BocNHNHBn[17,18] were reacted with epoxides **6**–**9** in refluxing $^i$PrOH-MeOH,[19] affording the target carbamate hydrazines **30**–**37** in 39–85% yield. The inclusion of methanol was essential to increase solubility. From NMR analysis, only one regioisomer was detected in each case. Lowest yields were obtained from the pyridin-3-yl-methyl-containing epoxide, that is epoxide **9**, where notable side reactions occurred.[20] The Boc-protected hydrazines **34**–**37** were reacted with TFA/$CH_2Cl_2$, yielding the free hydrazines, which were coupled with Boc-Val or Cbz-Val, vide supra, delivering the target hydrazides **38**–**45** in 49–96% yield over the deprotection and the coupling step (Scheme 3).

The Cbz-hydrazines **30**–**33** could not be prepared by the route starting from the Boc-hydrazines **34**–**37** (Scheme 3), that is Boc group cleavage and coupling with Z-Cl[21] due to the preferential formation of the corresponding six-membered ring-closed oxa-diazinanones.[22]

For the synthesis of all three additional stereoisomers of compound **32** (*R*,*R*), the stereoisomers of compound **1** (*R*,*R*) were used as starting materials. The *syn* ester **48** was prepared, starting with inversion of the hydroxyl group in the isopropylidene protected methyl ester **46**[11,13,23] (*R*,*R*) using Mitsunobu conditions with

**Table 1.** Biological activities of the most potent target compounds with *R,R* configuration at the central core

| Compd | Structure | Inh, Plm I (%)[a] | Inh, Plm II (%)[a] | $K_i$, Plm I (μM)[b] | $K_i$, Plm II (μM)[b] |
|---|---|---|---|---|---|
| **23** |  | 25 | 40 | ND | ND |
| **25** |  | 35 | 43 | ND | ND |
| **27** |  | 36 | 54 | ND | ND |
| **29** |  | 44 | 64 | ND | ND |
| **31** |  | 48 | 25 | ND | ND |
| **32** |  | 68 | 35 | >2 | >4.7 |
| **33** |  | 85 | 39 | 1.3 | ND |
| **40** |  | 57 | 49 | ND | ND |
| **45** |  | 48 | 50 | ND | ND |

[a]Inhibition at an inhibitor concentration of 5 μM.
[b]ND, not determined.

*p*-$NO_2$-benzoic acid, followed by cleavage of the obtained *p*-$NO_2$-benzoate ester with NaOMe to give the *syn* ester **47** (*S,R*) in 94% yield (Scheme 4). Subsequent alkylation with *p*-BrBnBr, using KI as catalyst, afforded the *p*-bromobenzylated *syn* ester **48** (*S,R*) in 98% yield. The *p*-bromobenzylated ester **50** (*R,S*) was prepared from commercially available methyl 3,4-*O*-isopropylidene-L-threonate (**49**) (*R,S*) in 96% yield, vide supra.

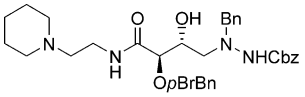
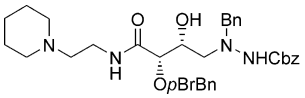
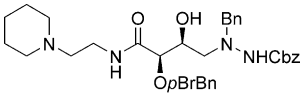
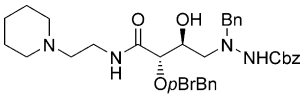
The alkylated esters **48** (*S,R*), **50** (*R,S*), and **51**[11] (*S,S*) were hydrolyzed and coupled with 1-(2-aminoethyl)-piperidine to give the amides **52** (*S,R*), **55** (*R,S*), and **58** (*S,S*) in 86–91% yield over two steps (Scheme 5). The subsequent deprotection and epoxide formation steps afforded the epoxides **53** (*S,R*), **56** (*R,S*), and **59** (S,S) in 82–87% overall yields. Finally, ring-opening with CbzNHNHBn yielded the target carbamate inhibitors **54** (*S,R*), **57** (*R,S*), and **60** (*S,S*) (73–89%).

## Biological data

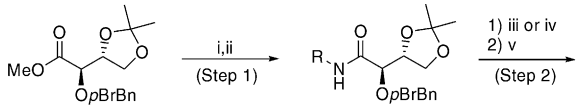
All final compounds were tested for their plasmepsin inhibitory properties, and the data of the most potent inhibitors are outlined in Tables 1 and 2. From analysis of the inhibition data, it appears that of the two sets of compounds synthesized, that is the *N*-benzyl- and the aza-benzyl core compounds, the *N*-benzyl derivatives were essentially inactive whereas the aza-benzyl derivatives, for example **32** and **33,** exhibited promising activity towards both both Plm I and II. Additionally, the presence of the benzylcarbamate group, either alone or coupled with valine, in the P2′ position seems to be beneficial in terms of potency. Regarding the the P2 substituents, the basic piperidine- and pyridine-substituents (C and D in Scheme 1) are incorporated in the majority of the most potent inhibitors.

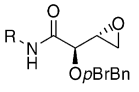
In order to assess the influence of chirality on inhibitor activity, the potent aza-based inhibitor (**32**) was selected

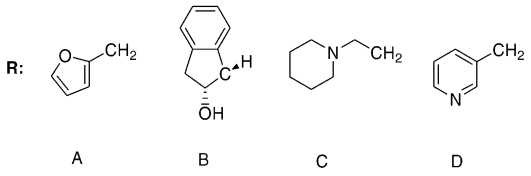
**Table 2.** Biological activities of compound **32** and its stereoisomers

| Compd | Structure | Inh, Plm I (%)[a] | Inh, Plm II (%)[a] | $K_i$, Plm I (μM)[b] | $K_i$, Plm II (μM)[b] |
|---|---|---|---|---|---|
| **32** |  | 68 | 35 | >2 | >4.7 |
| **54** |  | 55 | 35 | 0.82 | 3.0 |
| **57** |  | 98 | 74 | 0.25 | 1.4 |
| **60** |  | 57 | 20 | >2 | >4.7 |

[a]Inhibition at an inhibitor concentration of 5 μM.
[b]ND, not determined.



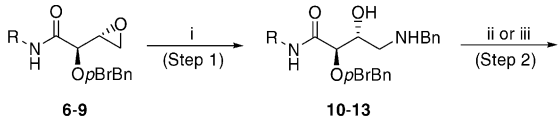



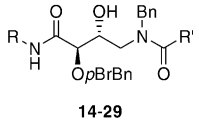




| R | Compd | Yield, step 1 | Compd | Yield, step 2 |
|---|---|---|---|---|
| A | **2** | 93 % | **6** | 70 %[a] |
| B | **3** | 81 % | **7** | 89 %[a] |
| C | **4** | 84 % | **8** | 86 %[b] |
| D | **5** | 86 % | **9** | 85 %[b] |

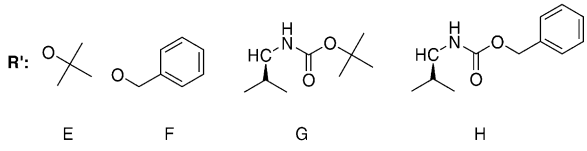
[a]Reagents iii were used for the deprotection of the isopropylidene group. [b]Reagents iv were used for the deprotection of the isopropylidene group.

**Scheme 1.** (i) LiOH, $H_2O$/dioxane, 0 °C; (ii) $RNH_2$, EDC, HOBt, TEA, DMF; (iii) Dowex $H^+$, MeOH; (iv) *p*-TsOH, MeOH; (v) DEAD, $Ph_3P$, $CHCl_3$, reflux.




**R:** As in Scheme 1



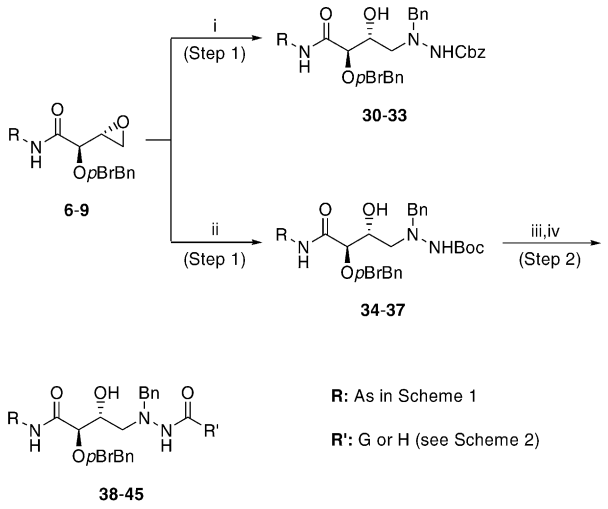

| R | Compd | Yield, step 1 | R' | Compd | Yield, step 2 |
|---|---|---|---|---|---|
| A | **10** | 90 % | E | **14** | 99 % |
| | | | F | **15** | 89 % |
| | | | G | **16** | 95 % |
| | | | H | **17** | 97 % |
| B | **11** | 93 % | E | **18** | 97 % |
| | | | F | **19** | 86 % |
| | | | G | **20** | 96 % |
| | | | H | **21** | 94 % |
| C | **12** | 86 % | E | **22** | 99 % |
| | | | F | **23** | 94 % |
| | | | G | **24** | 93 % |
| | | | H | **25** | 95 % |
| D | **13** | 82 % | E | **26** | 98 % |
| | | | F | **27** | 94 % |
| | | | G | **28** | 93 % |
| | | | H | **29** | 97 % |

**Scheme 2.** (i) $BnNH_2$, MeOH, 50 °C; (ii) $Boc_2O$ or Z-Cl, TEA, $CH_2Cl_2$; (iii) Boc-Val or Z-Val, HATU, DIEA, DMA.

and all stereoisomers (regarding the central core) of this inhibitor were synthesized. The plasmepsin inhibiting properties of compound **32** (*R,R*) together with the stereoisomeric inhibitors **54**, **57**, and **60** are presented in Table 2. $K_i$ values were determined for all three compounds **54** ($K_i = 820$ nM for Plm I and 3.0 μM for Plm II), **57** ($K_i = 250$ nM for Plm I and 1.4 μM for Plm II), and for **60** ($K_i > 2$ μM for Plm I and $> 4.7$ μM for Plm II).

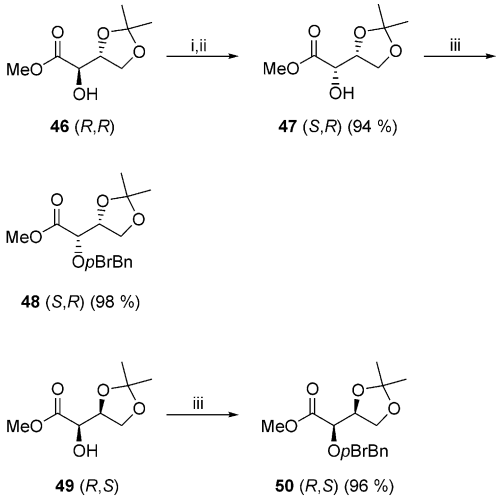
Changing the stereochemistry at the central core of inhibitor **32** proved to be beneficial with regard to plasmepsin affinity. Furthermore, there seems to be a trend towards a preference for Plm I over Plm II regarding the inhibitors in general in this report, and this observation is evidently even more significant for **54**, **57**, and **60**.

Somewhat surprisingly, the best inhibitor (**57**) in the whole series of target compounds presented in this report has the (*R,S*) *syn* configuration in the central part of the molecule. This fact gives rise to the opportunity to further optimize the present series of Plm I and II inhibitors.

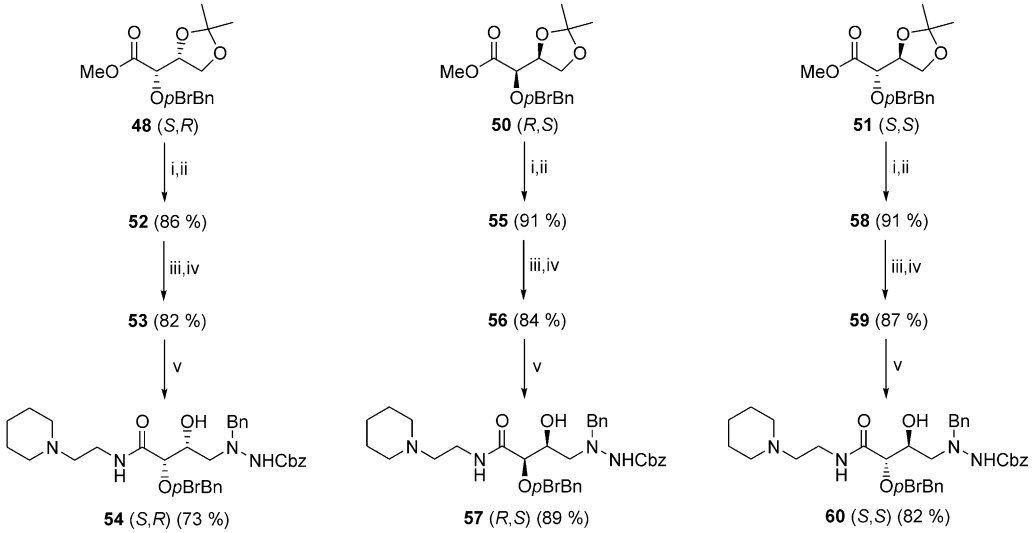



| R | Compd | Yield, step1 | R' | Compd | Yield, step2 |
|---|---|---|---|---|---|
| A | **30** | 80 % | - | - | - |
| B | **31** | 83 % | - | - | - |
| C | **32** | 84 % | - | - | - |
| D | **33** | 39 % | - | - | - |
| A | **34** | 73 % | G | **38** | 96 % |
| | | | H | **39** | 92 % |
| B | **35** | 85 % | G | **40** | 70 % |
| | | | H | **41** | 91 % |
| C | **36** | 78 % | G | **42** | 89 % |
| | | | H | **43** | 68 % |
| D | **37** | 48 % | G | **44** | 51 % |
| | | | H | **45** | 49 % |

**Scheme 3.** (i) CbzNHNHBn, $^i$PrOH, MeOH, reflux; (ii) BocNHNHBn, $^i$PrOH, MeOH, reflux; (iii) TFA, $CH_2Cl_2$; (iv) Boc-Val or Z-Val, HATU, DIEA, DMF.




**Scheme 4.** (i) *p*-$NO_2$-Benzoic acid, DEAD, $Ph_3P$, THF; (ii) NaOMe, MeOH; (iii) *p*-BrBnBr, $Ag_2O$, KI, toluene.




**Scheme 5.** Compare the synthesis of **32** (Schemes 1 and 3): (i) LiOH, $H_2O$/dioxane, 0 °C; (ii) 1-(2-aminoethyl)-piperidine, EDC, HOBt, TEA, DMF; (iii) *p*-TsOH, MeOH; (iv) DEAD, $Ph_3P$, $CHCl_3$, reflux; (v) CbzNHNHBn, $^i$PrOH, MeOH, reflux.

## Conclusions

We have identified new small lead inhibitors of the aspartic Plm I and II proteases based on carbohydrate-derived reversed-statine templates. The synthetic strategy allows for excellent control of the stereochemical properties of the intermediate compounds as well as the target compounds throughout the route. Additionally, the set of target compounds synthesized can easily be diversified using this methodology, which offers the opportunity to further optimize the plasmepsin inhibiting properties of the compounds presented. Some of the targets show promising activity against the plasmepsins, with the best inhibitor **57** having an in vitro activity of 98% inh@5 μM for Plm I and 74% inh@5 μM for Plm II, and with $K_i = 250$ nM for Plm I and 1.4 μM for Plm II.

## Experimental

### General methods

NMR spectra were recorded on a Varian 300 MHz instrument using $CDCl_3$ or MeOH-$d_4$ with TMS as an internal standard. Optical rotations were measured in $CHCl_3$ solutions on a Perkin-Elmer 141 polarimeter. TLC was carried out on Merck precoated 60 $F_{254}$ plates using UV-light and charring with EtOH/$H_2SO_4$/HOAc/*p*-anisaldehyde 90:3:1:2 for visualisation. Column chromatography was performed using silica gel 60 (0.040–0.063 mm, Merck). Organic phases were dried over anhydrous magnesium sulfate. Concentrations were performed under diminished pressure (1–2 kPa) at a bath temperature of 40 °C. The intermediate compounds **2**–**9**, **47**, **48**, **50**, **52**, **53**, **55**, **56**, **58**, and **59** were subjected to MALDI-TOF analysis, using a Voyager-DE STR Biospectrometry Workstation with α-cyano-4-hydroxycinnamic acid as reference. The LC–MS spectra of the target compounds were obtained using a Waters-micromass instrument equipped with a Waters 2790 pump, a Waters 996 diode array detector and a Waters ZMD MS detector. Column: Phenomenex Synergy max-rp 50×4.6 mm, C18, 4 μm, 80 Å. Eluent: Gradient using acqueous $NH_4HCO_3$ (10 mM) and $CH_3CN$. Flow: 1 mL/min. Wavelength: 254 nm.

### Plasmepsin assay measurements

Pro-plasmepsin II was generously provided from Helena Danielson (Department of Biochemistry, Uppsala University, Uppsala, Sweden). The expression and purification of plasmepsin I will be published elsewhere.[24] The activities of Plm I and Plm II were measured essentially as described previously,[9] using a total reaction volume of 100 μL. The concentration of pro-Plm II was 3 nM and the amount of Plm I was adjusted to give similar catalytic activity. The pro-sequence of Plm II was cleaved off by preincubation in an assay reaction buffer [100 mM sodium acetate buffer (pH 4.5), 10% glycerol and 0.01% Tween 20] at room temperature for 40 min. The reaction was initiated by the addition of 3 μM substrate (DABCYL-Glu-Arg-Nle-Phe-Leu-Ser-Phe-Pro-EDANS, AnaSpec Inc, San Jose, CA, USA) and hydrolysis was recorded as the increase in fluorescence intensity over a 10-min time period, during which the rate increased linearly with time. Stock solutions of inhibitors in DMSO were serially diluted in DMSO and added directly before addition of substrate, giving a final DMSO concentration of 1%.

$IC_{50}$ values were obtained by assuming competitive inhibition and fitting a Langmuir isotherm $[v_i/v_o = 1/(1 + [I]/IC_{50})]$ to the dose–response data (Grafit), where $v_i$ and $v_o$ are the initial velocities for the inhibited and uninhibited reaction, respectively, and [I] is the inhibitor concentration.[25] The $K_i$ was subsequently calculated by using $K_i = IC_{50}/(1 + [S]/K_m)$[26] and a $K_m$ value determined according to Michaelis–Menten.

### Synthetic experimentals

Unless otherwise noted, the compounds below were obtained as colorless solids.

Hydrolysis of methyl ester followed by peptide coupling to give the amides **2**–**5**, typical procedure: To an icecold solution of the methyl ester (1.15 mmol) in dioxane/$H_2O$ 1:1 (20 mL) was added aqueous LiOH (1 M, 1.50 mL, 1.50 mmol) dropwise during 5 min. The solution was stirred at 0 °C for an additional 45 min, after which the pH was adjusted to approximately 3. Saturation with $NH_4Cl$, several extractions with $CH_2Cl_2$, followed by drying, filtration, and evaporation of the organic phases provided the corresponding carboxylic acid which was used without further purification. The acid (1.15 mmol) was dissolved in DMF (10 mL) and the amine (1.72 mmol), 1-hydroxybenzotriazole (HOBt) (1.81 mmol), and $Et_3N$ (3.45 mmol) were added. The temperature was lowered to 0 °C and *N*′-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (EDC) (1.72 mmol) was added. The mixture was stirred at 0 °C for 1 h and then at rt overnight. The solvent was evaporated and the crude product was purified by flash column chromatography.

**(2*R*,3*R*)-2-(4-Bromobenzyloxy)-3,4-dihydroxy-*N*-(furan-2-yl-methyl)-3,4-*O*-isopropylidene-butyramide (2).** Compound **2** was synthesized in 93% yield from **1** (synthesized according to the methods described in refs 11 and 13) and furfurylamine. Chromatography eluent: toluene/ethyl acetate 4:1. **2**: $[\alpha]_D^{22}$ +37.5 (*c* 0.8, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz): δ 1.35 (s, 3H), 1.40 (s, 3H), 3.92 (dd, $J = 6.9$, 8.2 Hz, 1H), 3.96 (dd, $J = 6.9$, 8.2 Hz, 1H), 4.10 (d, $J = 3.3$ Hz, 1H), 4.38 (dd, $J = 5.6$, 16.0 Hz, 1H), 4.47 (dd, $J = 6.1$, 16.0 Hz, 1H), 4.51 (ddd, $J = 3.3$, 6.9, 6.9 Hz, 1H) 4.59 (d, $J = 11.7$ Hz, 1H), 4.69 (d, $J = 11.7$ Hz, 1H), 6.18 (dd, $J = 0.8$, 3.3 Hz, 1H), 6.32 (dd, $J = 1.9$, 3.3 Hz, 1H), 6.86 (m, 1H), 7.17 (d, $J = 8.5$ Hz, 2H), 7.35 (dd, $J = 0.8$, 1.9 Hz, 1H), 7.46 (d, $J = 8.5$ Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ 25.3, 26.3, 36.1, 64.6, 73.6, 76.9, 79.2, 107.7, 109.9, 110.6, 122.4, 129.9, 131.9, 136.0, 142.5, 150.9, 169.1. MS calcd for $C_{19}H_{22}BrNO_5Na$ $(M + Na)^+$: 446.06. Found: 446.01.

**(2*R*,3*R*)-2-(4-Bromobenzyloxy)-3,4-dihydroxy-*N*-((1*S*,2*R*)-2-hydroxy-indan-1-yl)-3,4-*O*-isopropylidene-butyramide**

**(3).** Compound **3** was synthesized in 81% yield from **1** and (1*S*,2*R*)-1-amino-2-indanol. Chromatography eluent: toluene/ethyl acetate 2:1. **3**: $[\alpha]_D^{22}$ +23.1 (*c* 0.3, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz): δ 1.36 (s, 3H), 1.45 (s, 3H), 2.64 (br s, 1H), 2.92 (dd, *J* = 2.1, 16.6 Hz, 1H), 3.15 (dd, *J* = 5.2, 16.6 Hz, 1H), 4.00 (dd, *J* = 6.8, 8.0 Hz, 1H), 4.04 (dd, *J* = 6.8, 8.0 Hz, 1H), 4.14 (d, *J* = 3.3 Hz, 1H), 4.50 (ddd, *J* = 3.3, 6.8, 6.8 Hz, 1H), 4.61 (ddd, *J* = 2.2, 5.2, 5.2 Hz, 1H); 4.65 (s, 2H), 5.14 (dd, *J* = 5.2, 8.5 Hz, 1H), 7.09–7.28 (m, 5H), 7.18 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 8.2 Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ 25.4, 26.3, 39.7, 57.4, 65.2, 73.1, 73.2, 77.0, 79.3, 110.0, 122.3, 124.3, 125.5, 127.3, 128.5, 129.8, 131.8, 135.9, 140.2, 140.3, 169.9. MS calcd for $C_{23}H_{26}BrNO_5Na$ $(M+Na)^+$: 498.09. Found: 498.05.

**(2*R*,3*R*)-2-(4-Bromobenzyloxy)-3,4-dihydroxy-3,4-*O*-isopropylidene-*N*-(2-piperidin-1-yl-ethyl)-butyramide (4).** Compound **4** was synthesized in 84% yield from **1** and 1-(2-aminoethyl)-piperidine. Chromatography eluent: toluene/ethyl acetate 1:1 + 1.5% $Et_3N$. **4**: $[\alpha]_D^{22}$ +34.1 (*c* 1.1, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz): δ 1.28 (s, 3H), 1.32–1.53 (m, 6H) 1.37 (s, 3H), 2.20–2.39 (m, 4H), 2.34 (t, *J* = 6.0 Hz, 2H), 3.13–3.37 (m, 2H), 3.87 (dd, *J* = 6.9, 8.1 Hz, 1H), 3.93 (dd, *J* = 6.9, 8.1 Hz, 1H), 4.03 (d, *J* = 3.3 Hz, 1H), 4.47 (ddd, *J* = 3.3, 6.9, 6.9 Hz, 1H), 4.56 (d, *J* = 11.8 Hz, 1H), 4.64 (d, *J* = 11.8 Hz, 1H), 7.10 (br s, 1H), 7.19 (d, *J* = 8.2 Hz, 2H), 7.41 (d, *J* = 8.2 Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ 24.3, 25.1, 25.9, 26.2, 35.6, 54.2, 56.9, 64.4, 73.1, 76.8, 79.1, 109.5, 121.9, 129.5, 131.6, 136.3, 168.9. MS calcd for $C_{21}H_{32}BrN_2O_4$ $(M+H)^+$: 455.16. Found: 455.12.

**(2*R*,3*R*)-2-(4-Bromobenzyloxy)-3,4-dihydroxy-3,4-*O*-isopropylidene-*N*-(pyridin-3-yl-methyl)-butyramide (5).** Compound **5** was synthesized in 86% yield from **1** and 3-aminomethylpyridine. Chromatography eluent: ethyl acetate/toluene 2:1 + 1.5% $Et_3N$. **5**: $[\alpha]_D^{22}$ +34.6 (*c* 0.9, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz): δ 1.28 (s, 3H), 1.33 (s, 3H), 3.85 (dd, *J* = 6.9, 8.0 Hz, 1H), 3.92 (dd, *J* = 6.9, 8.0 Hz, 1H), 4.06 (d, *J* = 3.3 Hz, 1H), 4.33 (dd, *J* = 6.2, 14.8 Hz, 1H), 4.41 (dd, *J* = 8.8, 14.8 Hz, 1H), 4.46 (ddd, *J* = 3.3, 6.9, 6.9 Hz, 1H), 4.53 (d, *J* = 11.8 Hz, 1H), 4.63 (d, *J* = 11.8 Hz, 1H), 7.05–7.21 (m, 2H), 7.09 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.45–7.52 (m, 1H), 8.19–8.25 (m, 2H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ 25.0, 26.2, 40.4, 64.6, 73.3, 76.7, 79.0, 109.7, 122.2, 123.5, 129.7, 131.7, 133.6, 135.3, 135.9, 148.9, 149.1, 169.3. MS calcd for $C_{20}H_{24}BrN_2O_4$ $(M+H)^+$: 435.09. Found: 435.04.

Isopropylidene group deprotection followed by epoxide formation to give the epoxides **6–9**, typical procedure: (A) Compounds with non-basic side chains: to a solution of the isopropylidene protected amide (0.36 mmol) in MeOH (5 mL) was added a suspension of Dowex $H^+$ (50×8, 20–50 mesh) in MeOH (3 mL) and the mixture was stirred at rt for 5 h. After filtration and evaporation the obtained product was dissolved in $CHCl_3$ (10 mL), and $Ph_3P$ (0.38 mmol) and diethylazodicarboxylate (DEAD) (0.38 mmol) were added. The solution was heated at reflux for 2 h, after which it was evaporated and the remainder was purified by flash column chromatography. (B) Compounds with basic side chains: to a solution of the isopropylidene protected amide (0.59 mmol) in MeOH was added *p*-TsOH (0.83 mmol) and the mixture was stirred at rt for 4 h. The solution was neutralized with $Et_3N$ and evaporated and the crude material was filtered through a short silica plug. The epoxide formation was then achieved as described above.

**(2*R*,3*R*)-2-(4-Bromobenzyloxy)-3,4-epoxy-*N*-(furan-2-yl-methyl)-butyramide (6).** Compound **6** was synthesized in 70% yield from **2**. Chromatography eluent: toluene/ethyl acetate 2:1. **6**: $[\alpha]_D^{22}$ +40.7 (*c* 0.6, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz): δ 2.70 (dd, *J* = 4.1, 5.2 Hz, 1H), 2.83 (dd, *J* = 2.5, 5.2 Hz, 1H), 3.42 (ddd, *J* = 2.0, 2.5, 4.1 Hz, 1H), 4.21 (d, *J* = 2.0 Hz, 1H), 4.35 (dd, *J* = 5.5, 15.7 Hz, 1H) 4.48 (dd, *J* = 6.0, 15.7 Hz, 1H), 4.49 (d, *J* = 11.8 Hz, 1H), 4.59 (d, *J* = 11.8 Hz, 1H), 6.19 (dd, *J* = 0.8, 3.3 Hz, 1H), 6.32 (dd, *J* = 1.9, 3.3 Hz, 1H), 6.86 (m, 1H), 7.14 (d, *J* = 8.2 Hz, 2H), 7.34 (dd, *J* = 0.8, 1.9 Hz, 1H), 7.45 (d, *J* = 8.2 Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ 36.1, 43.4, 52.2, 73.3, 77.1, 107.6, 110.5, 122.3, 129.8, 131.8, 135.8, 142.4, 150.8, 168.7. MS calcd for $C_{16}H_{17}BrNO_4$ $(M+H)^+$: 366.03. Found: 366.05.

**(2*R*,3*R*)-2-(4-Bromobenzyloxy)-3,4-epoxy-*N*-((1*S*,2*R*)-2-hydroxy-indan-1-yl)-butyramide (7).** Compound **7** was synthesized in 89% yield from **3**. Chromatography eluent: ethyl acetate/toluene 2:1. **7**: $[\alpha]_D^{22}$ +26.3 (*c* 0.8, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz): δ 2.74 (br s, 1H), 2.76 (dd, *J* = 4.4, 5.0 Hz, 1H), 2.88 (dd, *J* = 2.8, 5.0 Hz, 1H), 2.94 (dd, *J* = 1.9, 16.6 Hz, 1H), 3.14 (dd, *J* = 5.2, 16.6 Hz, 1H), 3.40 (ddd, *J* = 1.9, 2.8, 4.4 Hz, 1H), 4.30 (d, *J* = 1.9 Hz, 1H), 4.62 (m, 3H), 5.32 (dd, *J* = 5.0, 8.8 Hz, 1H), 7.05–7.16 (m, 3H), 7.19 (d, *J* = 8.2 Hz, 2H), 7.21–7.30 (m, 2H), 7.46 (d, *J* = 8.2 Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ 39.5, 44.2, 52.4, 57.7, 72.9, 73.1, 78.1, 122.4, 124.1, 125.5, 127.2, 128.5, 129.7, 131.9, 135.7, 139.9, 140.6, 169.0. MS calcd for $C_{20}H_{21}BrNO_4$ $(M+H)^+$: 418.07. Found: 418.12.

**(2*R*,3*R*)-2-(4-Bromobenzyloxy)-3,4-epoxy-*N*-(2-piperidin-1-yl-ethyl)-butyramide (8).** Compound **8** was synthesized in 86% yield from **4**. Chromatography eluent: ethyl acetate/MeOH 5:1 + 1% $Et_3N$. **8**: $[\alpha]_D^{22}$ +24.6 (*c* 1.0, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz): δ 1.31–1.55 (m, 6H), 2.23–2.40 (m, 4H), 2.37 (t, *J* = 6.0 Hz, 2H), 2.67 (dd, *J* = 4.1, 5.2 Hz, 1H), 2.83 (dd, *J* = 2.5, 5.2 Hz, 1H), 3.17–3.38 (m, 2H), 3.41 (ddd, *J* = 1.9, 2.5, 4.1 Hz, 1H), 4.15 (d, *J* = 1.9 Hz, 1H), 4.50 (d, *J* = 11.8 Hz, 1H), 4.59 (d, *J* = 11.8 Hz, 1H), 7.07–7.20 (m, 1H), 7.18 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 8.2 Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ 24.4, 26.1, 35.8, 43.4, 52.5, 54.4, 57.0, 73.2, 77.2, 122.1, 129.6, 131.8, 136.3, 168.7. MS calcd for $C_{18}H_{26}BrN_2O_3$ $(M+H)^+$: 397.11. Found: 397.09.

**(2*R*,3*R*)-2-(4-Bromobenzyloxy)-3,4-epoxy-*N*-(pyridin-3-yl-methyl)-butyramide (9).** Compound **9** was synthesized in 85% yield from **5**. Chromatography eluent: ethyl acetate + 1% $Et_3N$. **9**: $[\alpha]_D^{22}$ +37.5 (*c* 0.4, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz): δ 2.73 (dd, *J* = 4.1, 5.2 Hz, 1H), 2.83 (dd, *J* = 2.5, 5.2 Hz, 1H), 3.43 (ddd, *J* = 1.9, 2.5, 4.1 Hz, 1H), 4.25 (d, *J* = 1.9 Hz, 1H), 4.44 (d, *J* = 6.3 Hz, 2H), 4.50 (d, *J* = 11.5 Hz, 1H), 4.62 (d, *J* = 11.5 Hz,

1H), 6.98 (m, 1H), 7.14 (d, $J=8.2$ Hz, 2H), 7.20–7.28 (m, 1H), 7.44 (d, $J=8.2$ Hz, 2H), 7.48–7.60 (m, 1H), 8.49 (m, 2H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz): δ 40.6, 43.5, 52.2, 73.5, 77.2, 122.5, 123.7, 129.8, 131.9, 133.6, 135.5, 135.8, 149.2, 149.3, 169.0. MS calcd for $C_{18}H_{26}BrN_2O_3$ $(M+H)^+$: 377.05. Found: 377.03.

Epoxide opening with $BnNH_2$ to give compounds **10**–**13**, typical procedure: To a solution of the epoxide (0.88 mmol) in MeOH (15 mL) was added $BnNH_2$ (3.60 mmol) and the mixture was stirred at 50 C for 4 h. After evaporation the crude product was purified by flash column chromatography.

**(2*R*,3*R*)-4-Benzylamino-2-(4-bromobenzyloxy)-*N*-(furan-2-yl-methyl)-3-hydroxy-butyramide (10).** Compound **10** was synthesized in 90% yield from **6**. Chromatography eluent: $CHCl_3$/EtOH (99.5%) 97:3+2% MeOH satd with $NH_3$. **10**: $[\alpha]_D^{22}$ +35.9 (*c* 1.3, $CHCl_3$); $^1$H NMR ($CDCl_3$, 300 MHz): δ 2.64–2.78 (m, 2H), 2.90 (br s, 2H), 3.68 (d, $J=13.2$ Hz, 1H), 3.77 (d, $J=13.2$ Hz, 1H), 4.00 (m, 2H), 4.34 (dd, $J=5.3$, 15.5 Hz, 1H), 4.46 (dd, $J=6.0$, 15.5 Hz, 1H), 4.50 (d, $J=11.5$ Hz, 1H), 4.57 (d, $J=11.5$ Hz, 1H), 6.15 (dd, $J=0.8$, 3.3 Hz, 1H), 6.29 (dd, $J=1.9$, 3.3 Hz, 1H), 6.95–7.05 (m, 1H), 7.06 (d, $J=8.2$ Hz, 2H), 7.18–7.35 (m, 6H), 7.41 (d, $J=8.2$ Hz, 2H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz): δ 36.0, 49.7, 53.7, 70.8, 73.2, 81.0, 107.5, 110.5, 122.1, 127.0, 128.1, 128.4, 129.7, 131.7, 136.0, 139.8, 142.2, 150.8, 170.7. MS $(M+H)^+$: 473. Purity: 99%.

**(2*R*,3*R*)-4-Benzylamino-2-(4-bromobenzyloxy)-3-hydroxy-*N*-((1*S*,2*R*)-2-hydroxy-indan-1-yl)-butyramide (11).** Compound **11** was synthesized in 93% yield from **7**. Chromatography eluent: $CHCl_3$/EtOH (99.5%) 97:3+2% MeOH satd with $NH_3$. **7**: $[\alpha]_D^{22}$ +12.3 (*c* 0.5, $CHCl_3$); $^1$H NMR ($CDCl_3$, 300 MHz): δ 2.69–2.82 (m, 2H), 2.86 (dd, $J=1.9$, 16.6 Hz, 1H), 3.06 (dd, $J=5.3$, 16.6 Hz, 1H), 3.50 (br s, 2H), 3.65 (d, $J=13.2$ Hz, 1H), 3.72 (d, $J=13.2$ Hz, 1H), 3.93 (d, $J=3.6$ Hz, 1H), 3.96–4.05 (m, 1H), 4.47–4.53 (m, 1H), 4.49 (d, $J=11.8$ Hz, 1H), 4.58 (d, $J=11.8$ Hz, 1H), 5.25 (dd, $J=4.9$, 8.8 Hz, 1H), 7.11 (d, $J=8.5$ Hz, 2H), 7.16–7.33 (m, 9H), 7.40 (d, $J=8.5$ Hz, 2H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz): δ 39.3, 50.3, 53.5, 57.6, 71.1, 72.3, 72.5, 81.9, 122.1, 124.0, 125.3, 127.0, 127.1, 128.2, 128.3, 128.4, 129.6, 131.7, 135.8, 139.3, 140.0, 140.7, 170.9. MS $(M+H)^+$: 525. Purity: 99%.

**(2*R*,3*R*)-4-Benzylamino-2-(4-bromobenzyloxy)-3-hydroxy-*N*-(2-piperidin-1-yl-ethyl)-butyramide (12).** Compound **12** was synthesized in 86% yield from **8**. Chromatography eluent: $CHCl_3$/EtOH (99.5%) 9:1+2% MeOH satd with $NH_3$. **12**: $[\alpha]_D^{22}$ +29.8 (*c* 1.8, $CHCl_3$); $^1$H NMR ($CDCl_3$, 300 MHz): δ 1.35–1.55 (m, 6H), 2.22–2.41 (m, 6H), 2.75 (dd, $J=5.8$, 12.1 Hz, 1H), 2.81 (dd, $J=4.1$, 12.1 Hz, 1H), 3.29–3.39 (m, 2H), 3.72 (d, $J=13.2$ Hz, 1H), 3.81 (d, $J=13.2$ Hz, 1H), 3.92–4.01 (m, 2H), 4.52 (d, $J=11.8$ Hz, 1H), 4.58 (d, $J=11.8$ Hz, 1H), 7.04 (m, 1H), 7.17 (d, $J=8.2$ Hz, 2H), 7.20–7.37 (m, 5H), 7.44 (d, $J=8.2$ Hz, 2H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz): δ 24.3, 25.9, 35.7, 50.3, 53.9, 54.3, 57.3, 71.2, 72.8, 80.9, 122.0, 127.0, 128.2, 128.4, 129.6, 131.6, 136.2, 140.2, 171.0. MS $(M+H)^+$: 504. Purity: 98%.

**(2*R*,3*R*)-4-Benzylamino-2-(4-bromobenzyloxy)-3-hydroxy-*N*-(pyridin-3-yl-methyl)-butyramide (13).** Compound **13** was synthesized in 82% yield from **9**. Chromatography eluent: $CHCl_3$/EtOH (99.5%) 9:1+2% MeOH satd with $NH_3$. **13**: $[\alpha]_D^{22}$ +24.0 (*c* 1.0, $CHCl_3$); $^1$H NMR ($CDCl_3$, 300 MHz): δ 2.67 (dd, $J=4.7$, 12.4 Hz, 1H), 2.75 (dd, $J=6.6$, 12.4 Hz, 1H), 3.28 (br s, 1H), 3.64 (d, $J=13.2$ Hz, 1H), 3.72 (d, $J=13.2$ Hz, 1H), 3.96 (d, $J=4.4$ Hz, 1H), 4.03 (ddd, $J=4.4$, 4.7, 6.6 Hz, 1H), 4.35 (d, $J=6.0$ Hz, 2H) 4.45 (d, $J=11.8$ Hz, 1H), 4.52 (d, $J=11.8$ Hz, 1H), 7.05 (d, $J=8.5$ Hz, 2H), 7.12–7.32 (m, 8H), 7.35 (d, $J=8.5$ Hz, 2H), 7.46–7.52 (m, 1H), 8.38–8.42 (m, 2H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz): δ 40.3, 50.0, 53.6, 70.8, 72.8, 81.3, 122.0, 123.5, 127.0, 128.1, 128.3, 129.6, 131.6, 133.8, 135.4, 136.0, 139.7, 148.6, 148.8, 170.9. MS $(M+H)^+$: 484. Purity: 96%.

Carbamate formation to give compounds **14**, **15**, **18**, **19**, **22**, **23**, **26**, and **27**, typical procedure: To a solution of the secondary amine (0.13 mmol) in $CH_2Cl_2$ (3 mL) were added di-*tert*-butyl dicarbonate ($Boc_2O$) (0.14 mmol) or benzyl chloroformate (Z-Cl) (0.14 mmol) and $Et_3N$ (0.33 mmol) and the mixture was stirred at rt for 1 h. The solvent was evaporated and the crude product was purified by flash column chromatography.

Peptide coupling to give compounds **16**, **17**, **20**, **21**, **24**, **25**, **28**, and **29**, typical procedure: To a solution of the secondary amine (0.10 mmol) in DMF (3 mL) were added Boc-Val (0.14 mmol) or Cbz-Val (0.14 mmol) and *N*,*N*-diisopropylethylamine (DIEA) (0.30 mmol). The temperature was lowered to 0 °C and *O*-(7-aza-benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluroniumhexa-fluorophosphate (HATU) (0.11 mmol) was added. The mixture was stirred at 0 °C for 1 h and at rt for 1 h, after which the solvent was evaporated and the crude product was purified by flash column chromatography.

**(2*R*,3*R*)-2-(4-Bromobenzyloxy)-4-(*N*-*tert*-butyloxycarbonylbenzylamino)-*N*-(furan-2-yl-methyl)-3-hydroxy-butyramide (14).** Compound **14** was synthesized in 99% yield from **10** and $Boc_2O$. Chromatography eluent: $CHCl_3$. **14**: $[\alpha]_D^{22}$ −2.8 (*c* 0.9, $CHCl_3$); $^1$H NMR ($CDCl_3$, 300 MHz): δ 1.42 (s, 9H), 3.05–3.18 (m, 2H), 3.62 (br s, 1H), 3.92 (d, $J=4.4$ Hz, 1H), 4.15–4.23 (m, 2H), 4.36 (dd, $J=5.5$, 15.7 Hz, 1H), 4.45 (dd, $J=6.0$, 15.7 Hz, 1H), 4.47–4.65 (m, 3H), 6.15 (dd, $J=0.8$, 3.3 Hz, 1H), 6.26 (dd, $J=1.9$, 3.3 Hz, 1H), 6.97 (m, 1H), 7.09–7.21 (m, 2H), 7.14 (d, $J=8.2$ Hz, 2H), 7.24–7.36 (m, 4H), 7.43 (d, $J=8.2$ Hz, 2H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz): δ 28.6, 36.2, 49.7, 52.3, 73.0, 73.3, 81.2, 81.6, 107.6, 110.6, 122.3, 127.4, 128.7, 128.8, 129.9, 131.9, 132.0, 138.1, 142.4, 151.0, 156.9, 169.7. MS $(M+H)^+$: 573. Purity: 96%.

**(2*R*,3*R*)-4-(*N*-Benzyloxycarbonylbenzylamino)-2-(4-bromobenzyloxy)-*N*-(furan-2-yl-methyl)-3-hydroxy-butyramide (15).** Compound **15** was synthesized in 89% yield from **10** and Z-Cl. Chromatography eluent: $CHCl_3$. **15**: $[\alpha]_D^{22}$ +4.1 (*c* 1.2, $CHCl_3$); $^1$H NMR ($CDCl_3$, 300 MHz): δ 3.19–3.43 (m, 2H), 3.65 (br s, 1H), 3.80–3.98 (m, 2H), 4.14–4.27 (m, 1H), 4.27–4.70 (m, 5H), 5.16 (s, 2H), 6.15 (dd, $J=0.8$, 3.3 Hz, 1H), 6.28 (dd, $J=1.9$,

3.3 Hz, 1H), 6.90–7.08 (m, 1H), 7.14 (d, $J=8.2$ Hz, 2H), 7.18–7.37 (m, 11H), 7.43 (d, $J=8.2$ Hz, 2H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz): δ 35.9, 49.7, 51.6, 67.7, 72.4, 73.1, 81.3, 107.4, 110.4, 122.2, 127.4, 127.9, 128.1, 128.4, 128.5, 128.6, 129.1, 129.7, 129.8, 131.7, 137.2, 142.2, 150.6, 158.0, 169.5. MS $(M+H)^+$: 607. Purity: 98%.

**(2*R*,3*R*)-2-(4-Bromobenzyloxy)-4-[((*S*)-2-*N*-*tert*-butyloxycarbonylamino-3-methyl-butyryl)-benzylamino]-*N*-(furan-2-yl-methyl)-3-hydroxy-butyramide (16).** Compound **16** was synthesized in 95% yield from **10** and Boc-Val. Chromatography eluent: $CHCl_3$. 16: $[\alpha]_D^{22}$ −18.8 (*c* 0.9, $CHCl_3$); $^1$H NMR ($CDCl_3$, 300 MHz) (mixture of rotamers): δ 0.82–1.00 (m, 6H), 1.40 (s, 9H), 1.83–2.03 (m, 1H), 3.02–3.50 (m, 2H), 3.85–4.09 (m, 2H), 4.17–5.10 (m, 9H), 6.07–6.15 (m, 1H), 6.22–6.27 (m, 1H), 6.85–6.96 (m, 1H), 7.08–7.38 (m, 8H), 7.39–7.45 (m, 2H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz) (mixture of rotamers): δ 17.4, 18.3, 19.3, 19.5, 28.3, 31.3, 31.8, 35.9, 48.0, 48.2, 48.9, 55.3, 55.4, 69.9, 72.6, 73.3, 73.7, 79.6, 80.3, 81.5, 81.8, 107.4, 110.3, 110.4, 122.1, 122.3, 127.4, 127.9, 128.4, 128.5, 128.8, 129.7, 130.1, 131.7, 135.6, 135.7, 135.9, 137.2, 142.1, 150.7, 157.0, 169.0, 169.4, 173.1, 175.2. MS $(M+H)^+$: 672. Purity: 99%.

**(2*R*,3*R*)-4-[((*S*)-2-*N*-Benzyloxycarbonylamino-3-methyl-butyryl)-benzylamino]-2-(4-bromobenzyloxy)-*N*-(furan-2-yl-methyl)-3-hydroxy-butyramide (17).** Compound **17** was synthesized in 97% yield from **10** and Z-Val. Chromatography eluent: $CHCl_3$. 17: $[\alpha]_D^{22}$ −12.7 (*c* 0.5, $CHCl_3$); $^1$H NMR ($CDCl_3$, 300 MHz) (mixture of rotamers): δ 0.78–1.01 (m, 6H), 1.85–2.04 (m, 1H), 2.07 (br s, 1H), 3.02–3.65 (m, 2H), 3.78–5.75 (m, 11H), 6.07–6.15 (m, 1H), 6.22–6.29 (m, 1H), 6.87–7.01 (m, 1H), 7.05–7.46 (m, 15H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz) (mixture of rotamers): δ 17.2, 17.9, 19.4, 19.5, 31.3, 31.7, 35.9, 47.9, 48.1, 48.8, 52.3, 55.9, 56.0, 66.9, 67.1, 69.9, 72.4, 73.2, 73.7, 81.5, 81.7, 107.4, 110.3, 110.4, 122.1, 122.3, 127.3, 127.4, 127.9, 128.0, 128.1, 128.4, 128.5, 128.8, 129.7, 130.0, 131.6, 131.7, 135.6, 135.7, 135.8, 136.1, 137.0, 142.1, 150.6, 156.2, 157.2, 169.0, 169.4, 172.7, 174.5. MS $(M+H)^+$: 706. Purity: 98%.

**(2*R*,3*R*)-2-(4-Bromobenzyloxy)-4-(*N*-*tert*-butyloxycarbonylbenzylamino)-3-hydroxy-*N*-((1*S*,2*R*)-2-hydroxy-indan-1-yl)-butyramide (18).** Compound **18** was synthesized in 97% yield from **11** and $Boc_2O$. Chromatography eluent: $CHCl_3$. **18**: $[\alpha]_D^{22}$ −5.6 (*c* 1.2, $CHCl_3$); $^1$H NMR ($CDCl_3$, 300 MHz): δ 1.41 (s, 9H), 1.86 (br s, 1H), 2.92 (dd, $J=1.9$, 16.8 Hz, 1H), 3.12 (dd, $J=5.5$, 16.8 Hz, 1H) 3.21–3.38 (m, 2H), 3.45–3.61 (m, 1H), 3.91 (d, $J=3.3$ Hz, 1H), 4.11–4.67 (m, 6H), 5.12 (dd, $J=5.0$, 8.5 Hz, 1H), 7.05 (d, $J=8.5$ Hz, 1H), 7.09–7.36 (m, 9H), 7.15 (d, $J=8.2$ Hz, 2H), 7.43 (d, $J=8.2$ Hz, 2H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz): δ 28.5, 39.4, 50.0, 52.3, 57.9, 72.6, 72.7, 73.0, 81.0, 82.2, 122.1, 124.0, 125.5, 127.1, 127.4, 127.6, 128.4, 128.6, 129.7, 131.8, 135.9, 138.1, 139.9, 140.8, 157.8, 170.4. MS $(M+H)^+$: 625. Purity: 99%.

**(2*R*,3*R*)-4-(*N*-Benzyloxycarbonylbenzylamino)-2-(4-bromobenzyloxy)-3-hydroxy-*N*-((1*S*,2*R*)-2-hydroxy-indan-1-yl)-butyramide (19).** Compound **19** was synthesized in 86% yield from **11** and Z-Cl. Chromatography eluent: $CHCl_3$. **19**: $[\alpha]_D^{22}$ −3.8 (*c* 0.4, $CHCl_3$); $^1$H NMR ($CDCl_3$, 300 MHz): δ 1.38 (br s, 1H), 2.79–3.17 (m, 2H), 3.29–3.53 (m, 3H), 3.84–3.98 (m, 1H), 4.07–4.75 (m, 6H), 5.15, (s, 2H), 5.30 (dd, $J=5.0$, 8.6 Hz, 1H), 6.90–7.62 (m, 19H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz): δ 39.4, 50.1, 51.9, 57.8, 67.8, 71.9, 72.6, 72.7, 82.1, 122.3, 124.0, 125.4, 127.1, 127.5, 127.8, 128.0, 128.2, 128.3, 128.5, 128.6, 128.7, 129.7, 131.8, 135.8, 137.4, 139.8, 140.7, 157.8, 170.4. MS $(M+H)^+$: 659. Purity: 98%.

**(2*R*,3*R*)-2-(4-Bromobenzyloxy)-4-[((*S*)-2-*N*-*tert*-butyloxycarbonylamino-3-methyl-butyryl)-benzylamino]-3-hydroxy-*N*-((1*S*,2*R*)-2-hydroxy-indan-1-yl)-butyramide (20).** Compound **20** was synthesized in 96% yield from **11** and Boc-Val. Chromatography eluent: $CHCl_3$. **20**: $[\alpha]_D^{22}$ −6.6 (*c* 1.0, $CHCl_3$); $^1$H NMR ($CDCl_3$, 300 MHz) (mixture of rotamers): δ 0.80–1.01 (m, 6H), 1.40 (s, 9H), 1.85–2.01 (m, 1H), 2.10 (br s, 1H), 2.85–2.96 (m, 1H), 3.04–3.15 (m, 1H), 3.17–3.65 (m, 2H), 3.26–3.30 (m, 1H), 3.83–3.94 (m, 1H), 4.04–4.82 (m, 7H), 5.16–5.21 (m, 1H), 7.00–7.46 (m, 15H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz) (mixture of rotamers): δ 17.2, 17.4, 19.6, 19.8, 28.4, 31.6, 39.4, 40.0, 48.2, 48.5, 55.3, 57.6, 57.9, 69.7, 71.6, 72.0, 72.4, 72.6, 80.4, 81.8, 82.2, 122.3, 123.9, 124.1, 125.4, 127.1, 127.3, 127.5, 127.9, 128.0, 128.4, 128.5, 128.7, 128.9, 129.7, 131.7, 131.8, 135.7, 136.1, 137.1, 139.9, 140.8, 155.7, 157.0, 169.8, 170.2, 172.9. MS $(M+H)^+$: 724. Purity: 99%.

**(2*R*,3*R*)-4-[((*S*)-2-*N*-Benzyloxycarbonylamino-3-methyl-butyryl)-benzylamino]-2-(4-bromobenzyloxy)-3-hydroxy-*N*-((1*S*,2*R*)-2-hydroxy-indan-1-yl)-butyramide (21).** Compound 21 was synthesized in 94% yield from 11 and Z-Val. Chromatography eluent: $CHCl_3$. 21: $[\alpha]_D^{22}$ −5.1 (*c* 0.5, $CHCl_3$); $^1$H NMR ($CDCl_3$, 300 MHz) (mixture of rotamers): δ 0.80–1.22 (m, 6H), 1.88 (br s, 1H), 1.90–2.02 (m, 1H), 2.87–2.99 (m, 1H), 3.07–3.17 (m, 1H), 3.18–3.60 (m, 2H) 3.27–3.38 (m, 1H), 3.83–4.78 (m, 8H), 5.02–5.23 (m, 2H), 5.25–5.42 (m, 1H), 6.99–7.45 (m, 20H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz) (mixture of rotamers): δ 17.1, 17.3, 19.6, 19.8, 31.6, 38.8, 40.0, 48.1, 48.4, 49.2, 52.6, 55.9, 56.1, 57.6, 57.9, 67.1, 67.4, 71.8, 72.1, 72.4, 72.6, 72.7, 81.7, 82.2, 121.0, 122.2, 122.3, 123.9, 124.1, 125.5, 127.1, 127.2, 127.6, 128.0, 128.1, 128.2, 128.3, 128.4, 128.6, 128.8, 129.0, 129.5, 129.7, 129.8, 131.8, 131.8, 135.7, 135.8, 136.0, 137.0, 139.9, 140.7, 151.9, 156.3, 157.4, 169.7, 170.2, 172.5, 174.3. MS $(M+H)^+$: 758. Purity: 97%.

**(2*R*,3*R*)-2-(4-Bromobenzyloxy)-4-(*N*-*tert*-butyloxycarbonylbenzylamino)-3-hydroxy-*N*-(2-piperidin-1-yl-ethyl)-butyramide (22).** Compound **22** was synthesized in 99% yield from **12** and $Boc_2O$. Chromatography eluent: $CHCl_3$/EtOH (99.5%) 97:3 + 2% MeOH satd with $NH_3$. **22**: $[\alpha]_D^{22}$ +1.3 (*c* 0.8, $CHCl_3$); $^1$H NMR ($CDCl_3$, 300 MHz): δ 1.33–1.55 (m, 6H), 1.50 (s, 9H), 2.23–2.40 (m, 6H), 3.08–3.40 (m, 4H), 3.50–3.64 (m, 1H), 3.80–3.92 (m, 1H), 4.09–4.63 (m, 5H), 6.95–7.11 (m, 1H), 7.14–7.38 (m, 7H), 7.42 (d, $J=8.5$ Hz, 2H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz): δ 24.4, 25.9, 28.5, 35.8, 49.4, 51.9, 54.4, 57.3, 72.6, 72.8, 80.5, 81.7, 122.1, 127.3, 127.5, 128.6, 129.7, 131.7, 136.4, 138.3, 167.4, 170.0. MS $(M+H)^+$: 604. Purity: 100%.

**(2*R*,3*R*)-4-(*N*-Benzyloxycarbonylbenzylamino)-2-(4-bromobenzyloxy)-3-hydroxy-*N*-(2-piperidin-1-yl-ethyl)-butyramide (23).** Compound **23** was synthesized in 94% yield from **12** and Z-Cl. Chromatography eluent: $CHCl_3$/EtOH (99.5%) 97:3 + 2% MeOH satd with $NH_3$. **23**: $[\alpha]_D^{22}$ +5.6 (*c* 0.5, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz): δ 1.32–1.55 (m, 6H), 2.20–2.41 (m, 6H), 3.20–3.52 (m, 4H), 3.54–3.65 (m, 1H), 3.75–3.91 (m, 1H), 4.08–4.71 (m, 5H), 5.17 (s, 2H), 6.78–7.51 (m, 15H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ 24.3, 25.8, 35.7, 49.8, 51.6, 54.3, 57.3, 67.7, 72.2, 72.9, 81.6, 122.1, 127.4, 127.5, 128.0, 128.2, 128.5, 128.6, 128.8, 129.7, 131.7, 136.5, 137.8, 157.9, 170.0. MS $(M+H)^+$: 638. Purity: 99%.

**(2*R*,3*R*)-2-(4-Bromobenzyloxy)-4-[((*S*)-2-*N*-*tert*-butyloxycarbonylamino-3-methyl-butyryl)-benzylamino]-3-hydroxy-*N*-(2-piperidin-1-yl-ethyl)-butyramide (24).** Compound **24** was synthesized in 93% yield from **12** and Boc-Val. Chromatography eluent: $CHCl_3$/EtOH (99.5%) 97:3 + 2% MeOH satd with $NH_3$. **24**: $[\alpha]_D^{22}$ −11.9 (*c* 1.0, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz) (mixture of rotamers): δ 0.82–0.99 (m, 6H), 1.22–1.53 (m, 15H), 1.82–2.01 (m, 1H), 2.18–2.40 (m, 6H), 3.02–3.49 (m, 4H), 3.60–3.71 (m, 1H), 3.80–4.02 (m, 2H), 4.16–4.23 (m, 1H), 4.42–4.63 (m, 4H), 7.00–7.10 (m, 1H), 7.14–7.35 (m, 8H), 7.40–7.45 (m, 2H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz) (mixture of rotamers): δ 17.4, 18.0, 19.4, 19.6, 24.3, 25.8, 28.4, 31.5, 32.0, 35.7, 48.3, 48.4, 52.2, 54.3, 55.4, 57.2, 70.0, 72.3, 73.0, 73.1, 80.1, 82.0, 122.1, 122.2, 127.5, 128.0, 128.6, 128.9, 129.7, 130.0, 131.7, 136.0, 136.3, 137.4, 156.0, 156.9, 169.6, 169.9, 173.3, 174.6. MS $(M+H)^+$: 703. Purity: 99%.

**(2*R*,3*R*)-4-[((*S*)-2-*N*-Benzyloxycarbonylamino-3-methyl-butyryl)-benzylamino]-2-(4-bromobenzyloxy)-3-hydroxy-*N*-(2-piperidin-1-yl-ethyl)-butyramide (25).** Compound **25** was synthesized in 95% yield from **12** and Z-Val. Chromatography eluent: $CHCl_3$/EtOH (99.5%) 97:3 + 2% MeOH satd with $NH_3$. **25**: $[\alpha]_D^{22}$ −7.6 (*c* 0.8, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz) (mixture of rotamers): δ 0.80–1.00 (m, 6H), 1.27–1.52 (m, 6H), 1.83–2.02 (m, 1H), 2.17–2.41 (m, 6H), 3.03–3.37 (m, 4H), 3.58–3.66 (m, 1H), 3.78–4.01 (m, 2H), 4.15–4.24 (m, 1H), 4.42–4.87 (m, 4H), 4.98–5.17 (m, 2H), 6.98–7.09 (m, 1H), 7.11–7.43 (m, 15H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz) (mixture of rotamers): δ 17.3, 17.7, 19.3, 19.6, 24.3, 25.8, 31.6, 31.9, 35.7, 38.7, 48.2, 48.4, 52.1, 54.2, 56.0, 57.2, 57.3, 67.0, 67.1, 70.0, 72.2, 73.0, 81.9, 122.1, 122.2, 127.5, 127.6, 128.1, 128.2, 128.3, 128.6, 129.0, 129.7, 129.9, 131.7, 135.9, 136.2, 136.3, 137.3, 156.5, 157.1, 169.7, 169.8, 173.0, 174.3. MS $(M+H)^+$: 737. Purity: 99%.

**(2*R*,3*R*)-2-(4-Bromobenzyloxy)-4-(*N*-*tert*-butyloxycarbonylbenzylamino)-3-hydroxy-*N*-(pyridin-3-yl-methyl)-butyramide (26).** Compound **26** was synthesized in 98% yield from **13** and $Boc_2O$. Chromatography eluent: $CHCl_3$/EtOH (99.5%) 97:3 + 2% MeOH satd with $NH_3$. **26**: $[\alpha]_D^{22}$ −5.5 (*c* 0.6, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz): δ 1.42 (s, 9H), 3.07–3.22 (m, 2H), 3.49–3.62 (m, 1H), 3.92 (d, $J = 3.9$ Hz, 1H), 4.13–4.22 (m, 1H) 4.24–4.61 (m, 6H), 7.07–7.58 (m, 12H), 8.42–8.52 (m, 2H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ 28.5, 40.6, 49.8, 52.3, 72.7, 73.0, 81.0, 81.4, 122.3, 123.8, 127.5, 128.7, 128.8, 129.9, 131.9, 134.0, 135.8, 136.0, 138.0, 148.7, 148.9, 157.8, 170.1. MS $(M+H)^+$: 584. Purity: 99%.

**(2*R*,3*R*)-4-(*N*-Benzyloxycarbonylbenzylamino)-2-(4-bromobenzyloxy)-3-hydroxy-*N*-(pyridin-3-yl-methyl)-butyramide (27).** Compound **27** was synthesized in 94% yield from **13** and Z-Cl. Chromatography eluent: $CHCl_3$/EtOH (99.5%) 97:3 + 2% MeOH satd with $NH_3$. **27**: $[\alpha]_D^{22}$ −2.5 (*c* 1.0, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz): δ 3.18–3.45 (m, 2H), 3.52–3.63 (m, 1H), 3.84–3.95 (m, 1H), 4.19–4.25 (m, 1H), 4.30–4.62 (m, 6H), 5.16 (s, 2H), 6.93–7.58 (m, 17H), 8.42–8.52 (m, 2H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ 40.5, 50.0, 51.8, 67.9, 72.3, 73.0, 81.3, 122.3, 123.7, 127.0, 127.5, 128.0, 128.2, 128.6, 128.7, 129.8, 131.8, 133.8, 135.7, 136.1, 137.2, 148.6, 148.8, 158.0, 170.0. MS $(M+H)^+$: 618. Purity: 100%.

**(2*R*,3*R*)-2-(4-Bromobenzyloxy)-4-[((*S*)-2-*N*-*tert*-butyloxycarbonylamino - 3 - methyl - butyryl) - benzylamino] - 3 - hydroxy-*N*-(pyridin-3-yl-methyl)-butyramide (28).** Compound **28** was synthesized in 93% yield from **13** and Boc-Val. Chromatography eluent: $CHCl_3$/EtOH (99.5%) 97:3 + 2% MeOH satd with $NH_3$. **28**: $[\alpha]_D^{22}$ −18.3 (*c* 0.9, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz) (mixture of rotamers): δ 0.81–1.01 (m, 6H), 1.40 (s, 9H), 1.82–2.01 (m, 1H), 3.05–3.25 (m, 2H), 3.67–3.80 (m, 1H), 3.87–4.05 (m, 2H), 4.20–4.82 (m, 7H), 7.03–7.57 (m, 13H), 8.41–8.52 (m, 2H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz) (mixture of rotamers): δ 17.5, 18.3, 19.5, 19.6, 28.4, 31.4, 31.9, 40.5, 48.5, 48.6, 49.3, 52.6, 55.7, 70.1, 72.5, 73.2, 73.6, 80.2, 80.5, 81.6, 81.8, 122.3, 122.5, 123.8, 127.5, 127.6, 128.1, 128.5, 128.7, 129.0, 129.9, 130.1, 131.8, 131.9, 133.9, 134.0, 135.9, 137.3, 148.6, 148.7, 148.8, 156.0, 157.2, 169.7, 167.0, 173.3, 174.5. MS $(M+H)^+$: 683. Purity: 99%.

**(2*R*,3*R*)-4-[((*S*)-2-*N*-Benzyloxycarbonylamino-3-methyl-butyryl)-benzylamino]-2-(4-bromobenzyloxy)-3-hydroxy-*N*-(pyridin-3-yl-methyl)-butyramide (29).** Compound **29** was synthesized in 97% yield from **13** and Z-Val. Chromatography eluent: $CHCl_3$/EtOH (99.5%) 97:3 + 2% MeOH satd with $NH_3$. **29**: $[\alpha]_D^{22}$ −12.4 (*c* 0.9, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz) (mixture of rotamers): δ 0.82–1.00 (m, 6H), 1.84–2.03 (m, 1H), 3.07–3.25 (m, 2H), 3.62–3.75 (m, 1H), 3.88–4.06 (m, 2H), 4.21–4.82 (m, 7H), 4.98–5.20 (m, 2H), 7.05–7.55 (m, 18H), 8.41–8.50 (m, 2H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz) (mixture of rotamers): δ 17.3, 17.9, 19.3, 19.6, 31.4, 31.8, 40.5, 40.6, 48.4, 49.3, 52.6, 56.1, 56.2, 67.1, 67.3, 70.1, 72.4, 73.2, 73.6, 81.6, 122.4, 122.5, 123.8, 127.4, 127.7, 128.0, 128.1, 128.2, 128.4, 128.5, 128.6, 128.8, 129.1, 129.9, 130.1, 131.8, 131.9, 133.9, 135.8, 135.9, 136.0, 136.3, 137.2, 148.6, 148.8, 156.4, 156.4, 169.7, 170.0, 173.0, 174.8. HRMS calcd for $C_{37}H_{42}BrN_4O_6$ $(M+H)^+$: 717.2287. Found: 717.2282. Purity: 100%.

Epoxide opening with CbzNHNHBn or BocNHNHBn to give compounds **30**–**37**, typical procedure: To a solution of the epoxide (0.13 mmol) in $^i$PrOH (0.5 mL) and MeOH (1 mL) was added CbzNHNHBn (0.18 mmol) or BocNHNHBn (0.18 mmol), and the mixture

was refluxed overnight. The solvents were evaporated and the remainder was purified by flash column chromatography.

**(2*R*,3*R*)-4-(*N*-Benzyl-*N*′-benzyloxycarbonyl-hydrazino)-2-(4-bromobenzyloxy)-*N*-(furan-2-yl-methyl)-3-hydroxy-butyramide (30).** Compound **30** was synthesized in 80% yield from **6** and CbzNHNHBn. Chromatography eluent: toluene/ethyl acetate 2:1. **30**: $[\alpha]_D^{22}$ +14.2 (*c* 0.6, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz): δ 2.40 (br s, 1H), 2.67 (dd, *J* = 2.5, 12.2 Hz, 1H), 3.00 (dd, *J* = 10.2, 12.2 Hz, 1H), 3.83–4.05 (m, 2H) 4.07–4.13 (m, 1H), 4.14–4.22 (m, 1H), 4.36 (dd, *J* = 5.2, 15.5 Hz, 1H), 4.46 (dd, *J* = 6.1, 15.5 Hz, 1H), 4.55 (d, *J* = 11.5 Hz, 1H), 4.67 (d, *J* = 11.5 Hz, 1H), 5.01 (d, *J* = 12.1 Hz, 1H), 5.08 (d, *J* = 12.1 Hz, 1H), 5.80 (br s, 1H), 6.19 (dd, *J* = 0.8, 3.3 Hz, 1H), 6.32 (dd, *J* = 1.9, 3.3 Hz, 1H), 6.92–7.03 (m, 1H), 7.12 (d, *J* = 8.2 Hz, 2H), 7.13–7.33 (m, 10H), 7.35 (dd, *J* = 0.8, 1.9 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ 36.0, 58.1, 62.7, 67.2, 69.5, 73.2, 80.6, 107.5, 110.5, 122.1, 125.3, 127.9, 128.0, 128.5, 129.0, 129.3, 129.9, 131.7, 135.3, 135.9, 136.2, 142.2, 151.0, 156.7, 169.6. MS $(M+H)^+$: 622. Purity: 96%.

**(2*R*,3*R*)-4-(*N*-Benzyl-*N*′-benzyloxycarbonyl-hydrazino)-2-(4-bromobenzyloxy)-3-hydroxy-*N*-((1*S*,2*R*)-2-hydroxy-indan-1-yl)-butyramide (31).** Compound **31** was synthesized in 83% yield from **7** and CbzNHNHBn. Chromatography eluent: toluene/ethyl acetate 1:1. **31**: $[\alpha]_D^{22}$ +19.9 (*c* 0.7, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz): δ 2.39 (br s, 1H), 2.77–2.88 (m, 1H), 2.96 (dd, *J* = 1.9, 12.5 Hz, 1H), 3.03–3.18 (m, 2H), 3.88–4.12 (m, 4H), 4.52–4.69 (m, 3H), 5.04 (s, 2H), 5.36 (dd, *J* = 4.7, 8.8 Hz, 1H), 5.85 (br s, 1H), 7.06 (d, *J* = 8.8 Hz, 1H), 7.10–7.37 (m, 16H), 7.44 (d, *J* = 8.2 Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ 39.2, 58.1, 59.2, 62.7, 67.4, 69.9, 72.6, 72.7, 81.2, 122.3, 124.1, 125.4, 125.6, 127.2, 128.1, 128.2, 128.4, 128.6, 128.7, 129.2, 129.6, 129.8, 131.9, 135.1, 136.0, 139.9, 141.1, 157.1, 170.4. MS $(M+H)^+$: 674. Purity: 95%.

**(2*R*,3*R*)-4-(*N*-Benzyl-*N*′-benzyloxycarbonyl-hydrazino)-2-(4-bromobenzyloxy)-3-hydroxy-*N*-(2-piperidin-1-yl-ethyl)-butyramide (32).** Compound **32** was synthesized in 84% yield from **8** and CbzNHNHBn. Chromatography eluent: ethyl acetate/MeOH 5:1 + 1% $Et_3N$. **32**: $[\alpha]_D^{22}$ +10.5 (*c* 0.5, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz): δ 1.37–1.59 (m, 6H), 2.23–2.45 (m, 6H), 2.59 (br s, 1H), 2.67–3.07 (m, 2H), 3.25–3.39 (m, 2H), 3.85–4.21 (m, 4H), 4.50–4.71 (m, 2H), 5.00 (d, *J* = 12.4 Hz, 1H), 5.06 (d, *J* = 12.4 Hz, 1H), 5.85 (br s, 1H), 7.07–7.39 (m, 13H), 7.43 (d, *J* = 8.2 Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ 24.2, 25.7, 35.6, 54.3, 57.2, 58.0, 62.7, 67.0, 69.8, 72.9, 80.9, 121.9, 127.8, 128.0, 128.5, 128.6, 129.3, 129.5, 129.7, 131.6, 136.0, 136.3, 136.8, 156.5, 169.8. HRMS calcd for $C_{33}H_{42}BrN_4O_5$ $(M+H)^+$: 653.2338. Found: 653.2333. Purity: 99%.

**(2*R*,3*R*)-4-(*N*-Benzyl-*N*′-benzyloxycarbonyl-hydrazino)-2-(4-bromobenzyloxy)-3-hydroxy-*N*-(pyridin-3-yl-methyl)-butyramide (33).** Compound **33** was synthesized in 39% yield from **9** and CbzNHNHBn. Chromatography eluent: ethyl acetate + 1% $Et_3N$. **33**: $[\alpha]_D^{22}$ +7.1 (*c* 0.4, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz): δ 2.50 (br s, 1H), 2.63–2.75 (m, 1H), 3.00 (dd, *J* = 10.2, 12.4 Hz, 1H), 3.92 (d, *J* = 13.6 Hz, 1H), 4.01 (d, *J* = 13.6 Hz, 1H), 4.06–4.18 (m, 2H) 4.42 (dd, *J* = 6.1, 15.1 Hz, 1H), 4.50 (dd, *J* = 6.0, 15.1 Hz, 1H), 4.52–4.70 (m, 2H), 5.02 (d, *J* = 12.4 Hz, 1H), 5.07 (d, *J* = 12.4 Hz, 1H), 5.82 (br s, 1H), 7.11 (d, *J* = 8.2 Hz, 2H), 7.16–7.36 (m, 13H), 7.42 (d, *J* = 8.2 Hz, 2H), 8.46–8.60 (m, 2H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ 40.4, 58.4, 62.7, 67.2, 69.5, 73.1, 80.6, 122.2, 124.1, 127.9, 128.0, 128.3, 128.6, 129.4, 129.8, 129.9, 131.7, 131.9, 135.0, 135.6, 136.1, 137.1, 147.2, 147.6, 156.6, 170.4. HRMS calcd for $C_{32}H_{34}BrN_4O_5$ $(M+H)^+$: 633.1712. Found: 633.1707. Purity: 98%.

**(2*R*,3*R*)-4-(*N*-Benzyl-*N*′-*tert*-butyloxycarbonyl-hydrazino)-2-(4-bromobenzyloxy)-*N*-(furan-2-yl-methyl)-3-hydroxy-butyramide (34).** Compound **34** was synthesized in 73% yield from **6** and BocNHNHBn. Chromatography eluent: toluene/ethyl acetate 2:1. **34**: $[\alpha]_D^{22}$ +18.0 (*c* 0.6, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz): δ 1.35 (m, 9H), 2.55–2.66 (m, 1H), 2.97 (dd, *J* = 10.2, 12.4 Hz, 1H), 3.17 (br s, 1H), 3.80–4.03 (m, 2H), 4.08–4.22 (m, 2H), 4.36 (dd, *J* = 5.8, 15.4 Hz, 1H), 4.46 (dd, *J* = 6.0, 15.4 Hz, 1H), 4.57 (d, *J* = 11.5 Hz, 1H), 4.70 (d, *J* = 11.5 Hz, 1H), 5.45 (br s, 1H), 6.19 (dd, *J* = 0.8, 3.3 Hz, 1H), 6.32 (dd, *J* = 1.9, 3.3 Hz, 1H), 6.94–7.07 (m, 1H), 7.13 (d, *J* = 8.2 Hz, 2H), 7.18–7.36 (m, 6H), 7.43 (d, *J* = 8.2 Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ 28.3, 36.1, 58.1, 63.0, 69.6, 73.3, 80.4, 80.8, 107.5, 110.6, 122.1, 127.8, 128.5, 129.4, 130.0, 131.7, 135.8, 136.4, 142.3, 151.1, 156.4, 169.7. MS $(M+H)^+$: 588. Purity: 100%.

**(2*R*,3*R*)-4-(*N*-Benzyl-*N*′-*tert*-butyloxycarbonyl-hydrazino)-2-(4-bromobenzyloxy)-3-hydroxy-*N*-((1*S*,2*R*)-2-hydroxy-indan-1-yl)-butyramide (35).** Compound **35** was synthesized in 85% yield from **7** and BocNHNHBn. Chromatography eluent: toluene/ethyl acetate 1:1. **35**: $[\alpha]_D^{22}$ +16.9 (*c* 0.6, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz): δ 1.33 (s, 9H), 2.72–3.20 (m, 4H), 3.33 (br s, 1H), 3.80–4.13 (m, 3H), 4.01 (d, *J* = 1.9 Hz, 1H), 4.54–4.71 (m, 3H), 5.36 (dd, *J* = 8.8, 14.0 Hz, 1H), 5.58 (br s, 1H), 7.05–7.38 (m, 12H), 7.44 (d, *J* = 8.2 Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ 28.2, 39.2, 58.0, 59.1, 62.6, 69.9, 72.6, 72.7, 80.6, 81.3, 122.2, 124.1, 125.5, 127.1, 127.9, 128.5, 129.5, 130.2, 131.8, 132.1, 135.6, 136.1, 140.0, 141.0, 156.5, 170.4. MS $(M+H)^+$: 640. Purity: 98%.

**(2*R*,3*R*)-4-(*N*-Benzyl-*N*′-*tert*-butyloxycarbonyl-hydrazino)-2-(4-bromobenzyloxy)-3-hydroxy-*N*-(2-piperidin-1-yl-ethyl)-butyramide (36).** Compound **36** was synthesized in 78% yield from **8** and BocNHNHBn. Chromatography eluent: ethyl acetate/MeOH 9:1 + 1% $Et_3N$. **36**: $[\alpha]_D^{22}$ +12.7 (*c* 1.2, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz): δ 1.32 (s, 9H), 1.35–1.59 (m, 6H), 2.25–2.43 (m, 6H), 2.52 (br s, 1H), 2.60–2.70 (m, 1H), 2.98 (dd, *J* = 9.6, 12.4 Hz, 1H), 3.22–3.39 (m, 2H), 3.80–4.04 (m, 2H), 4.05–4.20 (m, 2H), 4.57 (d, *J* = 11.8 Hz, 1H), 4.69 (d, *J* = 11.8 Hz, 1H), 5.51 (br s, 1H), 7.18 (d, *J* = 8.2 Hz, 2H), 7.20–7.31 (m, 6H), 7.42 (d, *J* = 8.2 Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ 24.3, 25.9, 28.2, 35.7, 54.3, 57.2, 58.1, 62.8, 69.8, 73.0, 80.4, 81.0, 121.9, 127.7, 128.5, 129.5, 129.7, 131.6, 136.0, 136.7, 156.3, 169.8. MS $(M+H)^+$: 619. Purity: 97%.

**(2*R*,3*R*)-4-(*N*-Benzyl-*N'*-*tert*-butyloxycarbonyl-hydrazino)-2-(4-bromobenzyloxy)-3-hydroxy-*N*-(pyridin-3-yl-methyl)-butyramide (37).** Compound **37** was synthesized in 48% yield from **9** and BocNHNHBn. Chromatography eluent: ethyl acetate/MeOH 9:1 + 1% $Et_3N$. **37**: $[\alpha]_D^{22}$ +10.6 (*c* 0.8, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz): δ 1.37 (s, 9H), 2.57–2.67 (m, 1H), 2.97 (dd, *J* = 10.2, 12.2 Hz, 1H), 3.24 (br s, 1H), 3.80–4.01 (m, 2H), 4.05–4.20 (m, 2H), 4.38–4.47 (m, 2H), 4.56 (d, *J* = 11.8 Hz, 1H), 4.66 (d, *J* = 11.8 Hz, 1H), 5.58 (br s, 1H), 7.10 (d, *J* = 8.5 Hz, 2H), 7.14–7.53 (m, 10H), 8.42–8.54 (m, 2H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ 28.3, 40.5, 58.4, 63.0, 69.6, 73.1, 80.3, 80.8, 122.2, 123.8, 127.8, 128.5, 128.7, 129.4, 129.9, 131.9, 133.3, 134.1, 135.8, 148.8, 148.9, 156.6, 170.1. MS $(M+H)^+$: 599. Purity: 95%.

Deprotection of Boc-protected hydrazine followed by peptide coupling to give compounds **38**–**45**, typical procedure: To a solution of the Boc-protected hydrazine (0.18 mmol) in $CH_2Cl_2$ (1 mL) and TFA (1 mL) was added anisole (0.35 mmol) and the mixture was stirred at rt for 30 min. The volatiles were evaporated and the crude product was purified by flash column chromatography. The obtained deprotected hydrazine was then coupled to Boc-Val or Cbz-Val using the procedure described for compounds **16**, **17**, **20**, **21**, and so on.

**(2*R*,3*R*)-4-[*N*-Benzyl-*N'*-((*S*)-2-*tert*-butyloxycarbonyl-amino-3-methyl-butyryl)-hydrazino]-2-(4-bromobenzyloxy)-*N*-(furan-2-yl-methyl)-3-hydroxy-butyramide (38).** Compound **38** was synthesized in 96% yield from **34** and Boc-Val. Chromatography eluent: $CHCl_3$ + 2% MeOH satd with $NH_3$. **38**: $[\alpha]_D^{22}$ +12.7 (*c* 1.4, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz): δ 0.67–0.83 (m, 6H), 1.40 (s, 9H), 1.86–2.02 (m, 1H), 2.66–2.80 (m, 1H), 2.98 (dd, *J* = 10.3, 12.4 Hz, 1H) 3.61–3.70 (m, 1H), 3.96 (s, 2H), 4.02–4.18 (m, 2H), 4.34 (dd, *J* = 6.0, 15.4 Hz, 1H), 4.44–4.52 (m, 1H), 4.46 (dd, *J* = 6.2, 15.4 Hz, 1H), 4.54 (d, *J* = 11.5 Hz, 1H), 4.65 (d, *J* = 11.5 Hz, 1H), 4.82–4.92 (m, 1H), 6.18 (dd, *J* = 0.8, 3.3 Hz, 1H), 6.30 (dd, *J* = 1.9, 3.3 Hz, 1H), 6.94–7.05 (m, 1H), 7.11 (d, *J* = 8.2 Hz, 2H), 7.20–7.36 (m, 6H), 7.41 (d, *J* = 8.2 Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ 17.8, 19.3, 28.4, 30.4, 36.1, 38.7, 58.3, 62.3, 69.7, 73.1, 80.4, 80.8, 107.5, 110.6, 122.2, 127.9, 128.6, 129.3, 129.9, 131.7, 131.8, 136.4, 142.3, 151.2, 157.1, 169.7, 171.4. MS $(M+H)^+$: 687. Purity: 99%.

**(2*R*,3*R*)-4-[*N*-Benzyl-*N'*-((*S*)-2-benzyloxycarbonylamino-3-methyl-butyryl)-hydrazino]-2-(4-bromobenzyloxy)-*N*-(furan-2-yl-methyl)-3-hydroxy-butyramide (39).** Compound **39** was synthesized in 92% yield from **34** and Z-Val. Chromatography eluent: $CHCl_3$ + 2% MeOH satd with $NH_3$. **39**: $[\alpha]_D^{22}$ +8.2 (*c* 0.9, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz): δ 1.65–1.84 (m, 6H), 1.96–2.02 (m, 1H), 2.67–2.80 (m, 1H), 3.00 (dd, *J* = 9.6, 12.6 Hz, 1H), 3.15 (br s, 1H), 3.66–3.77 (m, 1H), 3.86–4.14 (m, 4H), 4.33 (dd, *J* = 5.9, 15.4 Hz, 1H), 4.45 (dd, *J* = 6.1, 15.4 Hz, 1H), 4.54 (d, *J* = 11.5 Hz, 1H), 4.66 (d, *J* = 11.5 Hz, 1H), 4.95–5.07 (m, 2H), 5.12–5.22 (m, 1H), 6.18 (dd, *J* = 0.8, 3.3 Hz, 1H), 6.30 (dd, *J* = 1.9, 3.3 Hz, 1H), 6.95–7.03 (m, 1H), 7.11 (d, *J* = 8.2 Hz, 2H), 7.20–7.37 (m, 12H), 7.40 (d, *J* = 8.2 Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ 17.8, 19.3, 30.4, 36.1, 38.7, 58.2, 62.3, 67.2, 69.8, 73.2, 80.7, 107.5, 110.6, 122.2, 127.9, 128.1, 128.3, 128.5, 128.7, 129.2, 129.6, 129.9, 131.8, 135.7, 136.4, 142.3, 151.1, 156.4, 169.8, 171.0. MS $(M+H)^+$: 721. Purity: 99%.

**(2*R*,3*R*)-4-[*N*-Benzyl-*N'*-((*S*)-2-*tert*-butyloxycarbonyl-amino-3-methyl-butyryl)-hydrazino]-2-(4-bromobenzyloxy)-3-hydroxy-*N*-((1*S*,2*R*)-2-hydroxy-indan-1-yl)-butyramide (40).** Compound **40** was synthesized in 70% yield from **35** and Boc-Val. Chromatography eluent: $CHCl_3$ + 2% MeOH satd with $NH_3$. **40**: $[\alpha]_D^{22}$ +7.9 (*c* 0.9, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz) (mixture of conformational isomers): δ 0.64–1.02 (m, 6H), 1.38–1.42 (m, 9H), 1.85–2.15 (m, 1H), 2.50 (m, 1H), 2.87–3.18 (m, 4H), 3.62–3.72 (m, 1H), 3.88–4.12 (m, 4H), 4.57 (d, *J* = 11.5 Hz, 1H), 4.58–4.62 (m, 1H), 4.63 (d, *J* = 11.5 Hz, 1H), 5.27–5.38 (m, 1H), 5.71 (br s, 1H), 6.13 (br s, 1H), 7.04–7.38 (m, 10H), 7.15 (d, *J* = 8.2 Hz, 1H), 7.42 (d, *J* = 8.2 Hz, 1H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz) (mixture of conformational isomers): δ 17.8, 19.3, 19.4, 20.1, 28.4, 28.5, 30.2, 30.8, 38.7, 39.3, 58.0, 59.3, 62.3, 69.9, 72.4, 72.7, 80.4, 80.7, 81.4, 82.4, 122.2, 124.0, 124.1, 125.6, 127.2, 128.0, 128.5, 128.6, 128.9, 129.4, 129.5, 129.7, 131.7, 131.8, 135.7, 136.1, 140.0, 141.1, 156.3, 157.2, 170.5, 171.0, 171.6. MS $(M+H)^+$: 739. HRMS calcd for $C_{37}H_{48}BrN_4O_7$ $(M+H)^+$: 739.2706. Found: 739.2701. Purity: 99%.

**(2*R*,3*R*)-4-[*N*-Benzyl-*N'*-((*S*)-2-benzyloxycarbonylamino-3-methyl-butyryl)-hydrazino]-2-(4-bromobenzyloxy)-3-hydroxy-*N*-((1*S*,2*R*)-2-hydroxy-indan-1-yl)-butyramide (41).** Compound **41** was synthesized in 91% yield from **35** and Z-Val. Chromatography eluent: $CHCl_3$ + 2% MeOH satd with $NH_3$. **41**: $[\alpha]_D^{22}$ +3.0 (*c* 0.8, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz) (mixture of conformational isomers): δ 0.62–1.01 (m, 6H), 1.82–2.18 (m, 1H), 2.48–2.59 (m, 1H), 2.87–3.18 (m, 4H), 3.66–3.78 (m, 1H), 3.84–4.13 (m, 4H), 4.42–4.68 (m, 3H), 4.95–5.17 (m, 2H), 5.13–5.17 (m, 1H), 5.69 (br s, 1H), 6.05 (br s, 1H), 6.98–7.45 (m, 15H), 7.14 (d, *J* = 8.2 Hz, 2H), 7.41 (d, *J* = 8.2 Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz) (mixture of conformational isomers): δ 16.4, 17.8, 19.4, 20.1, 30.3, 31.0, 38.7, 39.3, 58.0, 59.2, 62.3, 67.3, 67.5, 69.9, 72.5, 72.7, 81.5, 82.4, 122.2, 124.1, 125.6, 127.2, 128.1, 128.2, 128.4, 128.5, 128.6, 128.7, 128.9, 129.4, 129.7, 131.8, 136.2, 140.0, 141.0, 156.8, 170.5, 171.3, 173.8. MS $(M+H)^+$: 773. Purity: 99%.

**(2*R*,3*R*)-4-[*N*-Benzyl-*N'*-((*S*)-2-*tert*-butyloxycarbonyl-amino-3-methyl-butyryl)-hydrazino]-2-(4-bromobenzyloxy)-3-hydroxy-*N*-(2-piperidin-1-yl-ethyl)-butyramide (42).** Compound **42** was synthesized in 89% yield from **36** and Boc-Val. Chromatography eluent: ethyl acetate/MeOH 9:1 + 1% $Et_3N$. **42**: $[\alpha]_D^{22}$ +8.3 (*c* 0.8, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz) (mixture of conformational isomers): δ 0.65-0-99 (m, 6H), 1.34–1.63 (m, 15H), 1.86–2.00 (m, 1H), 2.10 (m, 1H), 2.25–2.54 (m, 6H), 2.81–3.12 (m, 2H), 3.22–3.42 (m, 2H), 3.60–3.71 (m, 1H), 3.93–4.14 (m, 4H), 4.58 (d, *J* = 11.5 Hz, 1H), 4.65 (d, *J* = 11.5 Hz, 1H), 4.82–4.95 (m, 1H), 6.60 (br s, 1H), 7.03 (br s, 1H), 7.18 (d, *J* = 8.2 Hz, 2H), 7.20–7.35 (m, 5H), 7.43 (d, *J* = 8.2 Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz) (mixture of conformational isomers): δ 17.8, 19.3, 24.3, 25.9, 28.4, 28.5, 30.4, 35.7, 54.3, 54.4, 57.0, 57.3, 58.2, 59.0,

62.1, 70.0, 72.9, 80.3, 80.9, 81.3, 121.9, 127.9, 128.4, 128.6, 128.7, 128.8, 129.3, 129.4, 129.6, 129.7, 129.8, 131.6, 131.7, 135.8, 136.7, 156.1, 169.9, 171.2, 171.4. MS $(M+H)^+$: 718. Purity: 95%.

**(2*R*,3*R*)-4-[*N*-Benzyl-*N*′-((*S*)-2-benzyloxycarbonylamino-3-methyl-butyryl)-hydrazino]-2-(4-bromobenzyloxy)-3-hydroxy-*N*-(2-piperidin-1-yl-ethyl)-butyramide (43).** Compound **43** was synthesized in 68% yield from **36** and Z-Val. Chromatography eluent: ethyl acetate/MeOH 9:1 + 1% $Et_3N$. **43**: $[\alpha]_D^{22}$ +6.4 (*c* 0.8, $CHCl_3$); $^1H$ NMR (MeOH-$d_4$, 300 MHz): δ 0.64–0.78 (m, 6H), 1.38–1.62 (m, 6H), 1.72–1.86 (m, 1H), 2.34–2.52 (m, 6H), 2.85–2.99 (m, 2H), 3.30–3.39 (m, 1H), 3.80–4.09 (m, 4H), 4.54 (s, 2H), 4.98 (d, *J* = 12.6 Hz, 1H), 5.04 (d, *J* = 12.6 Hz, 1H), 7.13–7.38 (m, 12H), 7.45 (d, *J* = 8.5 Hz, 2H); $^{13}C$ NMR (MeOH-$d_4$, 75.5 MHz): δ 17.3, 18.4, 23.9, 25.4, 30.5, 35.7, 54.3, 57.4, 59.1, 59.9, 61.8, 66.5, 69.7, 72.1, 81.6, 121.5, 127.4, 127.6, 127.7, 127.8, 128.1, 128.3, 129.3, 129.9, 131.3, 136.8, 137.2, 156.5, 171.2, 171.9. MS $(M+H)^+$: 752. Purity: 99%.

**(2*R*,3*R*)-4-[*N*-Benzyl-*N*′-((*S*)-2-*tert*-butyloxycarbonylamino-3-methyl-butyryl)-hydrazino]-2-(4-bromobenzyloxy)-3-hydroxy-*N*-(pyridin-3-yl-methyl)-butyramide (44).** Compound **44** was synthesized in 51% yield from **37** and Boc-Val. Chromatography eluent: ethyl acetate/MeOH 9:1 + 1% $Et_3N$. **44**: $[\alpha]_D^{22}$ +4.5 (*c* 0.5, $CHCl_3$); $^1H$ NMR (MeOH-$d_4$, 300 MHz): δ 0.63–0.75 (m, 6H), 1.40 (s, 9H), 1.67–1.80 (m, 1H), 2.89–3.00 (m, 2H), 3.59–3.66 (m, 1H), 3.85 (d, *J* = 13.2 Hz, 1H), 3.96 (d, *J* = 13.2 Hz, 1H), 3.99–4.10 (m, 2H), 4.40 (d, *J* = 13.2 Hz, 1H), 4.46 (d, *J* = 13.2 Hz, 1H), 4.52 (d, *J* = 11.8 Hz, 1H), 4.59 (d, *J* = 11.8 Hz, 1H), 7.16–7.41 (m, 8H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.73–7.79 (m, 1H), 8.38–8.52 (m, 2H); $^{13}C$ NMR (MeOH-$d_4$, 75.5 MHz): δ 17.2, 18.4, 27.5, 30.7, 40.0, 59.2, 59.5, 61.7, 69.7, 72.0, 80.9, 81.5, 121.5, 124.0, 127.4, 128.1, 129.3, 130.0, 131.3, 135.4, 136.4, 136.8, 137.0, 147.6, 148.2, 156.8, 171.6, 172.0. MS $(M+H)^+$: 698. Purity: 96%.

**(2*R*,3*R*)-4-[*N*-Benzyl-*N*′-((*S*)-2-benzyloxycarbonylamino-3-methyl-butyryl)-hydrazino]-2-(4-bromobenzyloxy)-3-hydroxy-*N*-(pyridin-3-yl-methyl)-butyramide (45).** Compound **45** was synthesized in 49% yield from **37** and Z-Val. Chromatography eluent: ethyl acetate/MeOH 9:1 + 1% $Et_3N$. **45**: $[\alpha]_D^{22}$ +2.2 (*c* 1.1, $CHCl_3$); $^1H$ NMR (MeOH-$d_4$, 300 MHz): δ 0.69 (d, *J* = 6.9 Hz, 3H), 0.74 (d, *J* = 6.7 Hz, 3H), 1.69–1.82 (m, 1H), 2.85–3.00 (m, 2H), 3.63–3.67 (m, 1H), 3.85 (d, *J* = 13.7 Hz, 1H), 3.95 (d, *J* = 13.7 Hz, 1H), 4.00–4.09 (m, 2H), 4.39 (d, *J* = 13.5 Hz, 1H), 4.45 (d, *J* = 13.5 Hz, 1H), 4.50 (d, *J* = 11.8 Hz, 1H), 4.57 (d, *J* = 11.8 Hz, 1H), 4.97 (d, *J* = 12.4 Hz, 1H), 5.05 (d, *J* = 12.4 Hz, 1H), 7.13–7.46 (m, 13H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.72–7.79 (m, 1H), 8.38–8.52 (m, 2H); $^{13}C$ NMR (MeOH-$d_4$, 75.5 MHz): δ 17.3, 18.4, 30.5, 40.0, 59.4, 59.9, 61.8, 66.5, 69.7, 72.0, 81.4, 121.5, 124.0, 127.4, 127.6, 127.8, 128.0, 128.2, 128.3, 129.3, 130.0, 131.3, 135.4, 136.4, 136.8, 137.0, 147.6, 148.2, 157.2, 171.6, 171.9. MS $(M+H)^+$: 732. Purity: 97%.

**Methyl (2*S*,3*R*)-3,4-*O*-isopropylidene-2,3,4-trihydroxy-butyrate (47).** To a solution of compound **46** (synthesized according to the methods desribed in refs 11 and 13) (0.580 g, 3.05 mmol) in dry THF (10 mL) were added *p*-nitrobenzoic acid (0.82 g, 4.91 mmol) and $Ph_3P$ (1.27 g, 4.85 mmol). The reaction flask was placed in a water bath at room temperature, and a solution of diethyl azodicarboxylate (DEAD) (0.77 mL, 0.860 g, 4.94 mmol) in dry THF (10 mL) was added dropwise to the stirred solution during half an hour at room temperature. The reaction solution was stirred overnight at room temperature and was then evaporated and purified by flash column chromatography (toluene/EtOAc 6:1). The product was dissolved in MeOH (15 mL) and was subsequently reacted with NaOMe in MeOH (1 M, 1.5 mL, 1.5 mmol), which was slowly added dropwise into the stirred solution at room temperature. The solution was stirred at room temperature for an additional 30 min, after which it was neutralized with HOAc, evaporated, and purified by flash column chromatography (toluene/EtOAc 6:1). This afforded compound **47** (0.543 g, 94%) as a colorless oil (cf. ref 11). **47**: $[\alpha]_D^{22}$ −19.1 (*c* 0.5, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz): δ 1.23 (s, 3H), 1.30 (s, 3H), 3.09 (br s, 1H), 3.68 (s, 3H), 3.88 (dd, *J* = 6.8, 8.2 Hz, 1H), 3.96 (dd, *J* = 6.8, 8.2 Hz, 1H), 4.03 (d, *J* = 3.0 Hz, 1H), 4.27 (ddd, *J* = 3.0, 6.8, 6.8 Hz, 1H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ 25.1, 25.9, 52.5, 65.4, 70.3, 76.2, 109.8, 172.4. MS calcd for $C_8H_{15}O_5$ $(M+H)^+$: 191.09. Found: 191.06.

**Methyl (2*S*,3*R*)-2-(4-bromobenzyloxy)-3,4-dihydroxy-3,4-*O*-isopropylidene- butyrate (48).** To a solution of compound **47** (0.455 g, 2.39 mmol) in toluene (10 mL) were added *p*-bromobenzyl bromide (2.12 g, 8.47 mmol), $Ag_2O$ (1.68 g, 7.27 mmol), and KI (67 mg, 0.41 mmol) and the mixture was stirred at room temperature for 15 min (some heat evolution was observed). The suspension was filtered, evaporated, and purified by flash column chromatography (toluene/EtOAc 6:1) to give compound **48** (0.84 g, 98%). (cf. ref 11). **48**: $[\alpha]_D^{22}$ −46.4 (*c* 2.3, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz): δ 1.28 (s, 3H), 1.33 (s, 3H), 3.70 (s, 3H), 3.89 (dd, *J* = 6.0, 8.8 Hz, 1H), 3.92 (d, *J* = 6.0 Hz, 1H) 3.96 (dd, *J* = 6.0, 8.8 Hz, 1H), 4.34 (ddd, *J* = 6.0, 6.0, 6.0 Hz, 1H), 4.40 (d, *J* = 11.8 Hz, 1H), 4.65 (d, *J* = 11.8 Hz, 1H), 7.18 (d, *J* = 8.2 Hz, 2H), 7.39 (d, *J* = 8.2 Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ 25.2, 26.2, 52.0, 65.4, 71.9, 75.7, 78.7, 109.8, 121.7, 129.6, 131.4, 136.2, 170.2. MS calcd for $C_{15}H_{19}BrO_5K$ $(M+K)^+$: 397.01. Found: 397.05.

**Methyl (2*R*,3*S*)-2-(4-bromobenzyloxy)-3,4-dihydroxy-3,4-*O*-isopropylidene- butyrate (50).** Compound **50** was synthesized in 96% yield from methyl 3,4-*O*-isopropylidene-L-threonate (**49**) according to the procedure for preparing **48**. **50**: $[\alpha]_D^{22}$ +47.3 (*c* 0.7, $CHCl_3$); NMR data: See compound **48**. MS calcd for $C_{15}H_{19}BrO_5K$ $(M+K)^+$: 397.01. Found: 397.07.

**(2*S*,3*R*)-2-(4-Bromobenzyloxy)-3,4-dihydroxy-3,4-*O*-isopropylidene-*N*-(2-piperidin-1-yl-ethyl)-butyramide (52).** Compound **52** was synthesized in 86% yield from **48** and 1-(2-aminoethyl)-piperidine according to the procedure for preparing **4**. Chromatography eluent: toluene/ethyl acetate 1:1 + 1.5% $Et_3N$. **52**: $[\alpha]_D^{22}$ −30.3 (*c* 2.3, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz): δ 1.27 (s, 3H),

1.30–1.49 (m, 6H) 1.35 (s, 3H), 2.20–2.39 (m, 4H), 2.34 (t, $J=6.0$ Hz, 2H), 3.15–3.37 (m, 2H), 3.73 (d, $J=6.2$ Hz, 1H), 3.95 (dd, $J=6.2$ Hz, 8.8 Hz, 1H), 3.98 (dd, $J=6.2$ Hz, 8.8 Hz, 1H), 4.22 (ddd, $J=6.2$, 6.2, 6.2 Hz, 1H), 4.54 (d, $J=11.8$ Hz, 1H), 4.60 (d, $J=11.8$ Hz, 1H), 7.14 (m, 1H), 7.20 (d, $J=8.2$ Hz, 2H), 7.41 (d, $J=8.2$ Hz, 2H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz): δ 24.3, 25.5, 26.0, 26.4, 35.6, 54.2, 57.0, 66.1, 72.7, 76.8, 81.0, 109.4, 121.9, 129.5, 131.5, 136.2, 169.3. MS calcd for $C_{21}H_{32}BrN_2O_4$ $(M+H)^+$: 455.16. Found: 455.20.

**(2*S*,3*R*)-2-(4-Bromobenzyloxy)-3,4-epoxy-*N*-(2-piperidin-1-yl-ethyl)-butyramide (53).** Compound **53** was synthesized in 82% yield from **52** according to the procedure for preparing **8**. Chromatography eluent: ethyl acetate/MeOH 5:1 + 1% $Et_3N$. **53**: $[\alpha]_D^{22}$ −7.5 (*c* 0.7, $CHCl_3$); $^1$H NMR ($CDCl_3$, 300 MHz): δ 1.34–1.57 (m, 6H), 2.28–2.44 (m, 4H), 2.42 (t, $J=6.0$ Hz, 2H), 2.81–2.87 (m, 2H), 3.13–3.20 (m, 1H), 3.21–3.44 (m, 2H), 3.59 (d, $J=6.3$ Hz, 1H), 4.57 (d, $J=11.8$ Hz, 1H), 4.72 (d, $J=11.8$ Hz, 1H), 7.20–7.31 (m, 1H), 7.23 (d, $J=8.5$ Hz, 2H), 7.45 (d, $J=8.5$ Hz, 2H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz): δ 24.3, 26.0, 35.7, 44.0, 53.2, 54.2, 56.9, 71.7, 81.2, 122.0, 129.5, 131.6, 136.1, 168.3. MS calcd for $C_{18}H_{26}BrN_2O_3$ $(M+H)^+$: 397.11. Found: 397.11.

**(2*S*,3*R*)-4-(*N*-Benzyl-*N*′-benzyloxycarbonyl-hydrazino)-2-(4-bromobenzyloxy)-3-hydroxy-*N*-(2-piperidin-1-yl-ethyl)-butyramide (54).** Compound **54** was synthesized in 73% yield from **53** and CbzNHNHBn according to the procedure for preparing **32**. Chromatography eluent: ethyl acetate/MeOH 5:1 + 1% $Et_3N$. **54**: $[\alpha]_D^{22}$ −29.1 (*c* 0.7, $CHCl_3$); $^1$H NMR ($CDCl_3$, 300 MHz): δ 1.38–1.67 (m, 6H), 2.26–2.84 (m, 7H), 2.81 (dd, $J=5.2$, 12.9 Hz, 1H), 2.85–3.16 (m, 1H), 3.18–3.75 (m, 2H), 3.83–4.17 (m, 4H), 4.26–4.65 (m, 2H), 4.97–5.07 (m, 2H), 6.01 (br s 1H), 7.03–7.40 (m, 13H), 7.43 (d, $J=8.2$ Hz, 2H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz): δ 24.0, 25.4, 35.6, 54.4, 57.9, 58.6, 62.4, 67.0, 69.4, 72.6, 80.7, 122.2, 127.8, 128.1, 128.3, 128.6, 129.5, 129.6, 130.0, 131.7, 132.0, 136.1, 136.3, 156.4, 171.2. HRMS calcd for $C_{33}H_{42}BrN_4O_5$ $(M+H)^+$: 653.2338. Found: 653.2333. Purity: 99%.

**(2*R*,3*S*)-2-(4-Bromobenzyloxy)-3,4-dihydroxy-3,4-*O*-isopropylidene-*N*-(2-piperidin-1-yl-ethyl)-butyramide (55).** Compound **55** was synthesized in 91% yield from **50** and 1-(2-aminoethyl)-piperidine according to the procedure for preparing **4**. Chromatography eluent: toluene/ethyl acetate 1:1 + 1.5% $Et_3N$. **55**: $[\alpha]_D^{22}$ +31.2 (*c* 1.3, $CHCl_3$); NMR data: See compound **52**. MS calcd for $C_{21}H_{32}BrN_2O_4$ $(M+H)^+$: 455.16. Found: 455.11.

**(2*R*,3*S*)-2-(4-Bromobenzyloxy)-3,4-epoxy-*N*-(2-piperidin-1-yl-ethyl)-butyramide (56).** Compound **56** was synthesized in 84% yield from **55** according to the procedure for preparing **8**. Chromatography eluent: ethyl acetate/MeOH 5:1 + 1% $Et_3N$. **56**: $[\alpha]_D^{22}$ +7.1 (*c* 0.7, $CHCl_3$); NMR data: See compound **53**. MS calcd for $C_{18}H_{26}BrN_2O_3$ $(M+H)^+$: 397.11. Found: 397.10.

**(2*R*,3*S*)-4-(*N*-Benzyl-*N*′-benzyloxycarbonyl-hydrazino)-2-(4-bromobenzyloxy)-3-hydroxy-*N*-(2-piperidin-1-yl-ethyl)-butyramide (57).** Compound **57** was synthesized in 89% yield from **56** and CbzNHNHBn according to the procedure for preparing **32**. Chromatography eluent: ethyl acetate/MeOH 5:1 + 1% $Et_3N$. **57**: $[\alpha]_D^{22}$ +30.0 (*c* 1.1, $CHCl_3$); NMR data: See compound **54**. HRMS calcd for $C_{33}H_{42}BrN_4O_5$ $(M+H)^+$: 653.2338. Found: 653.2333. Purity: 99%.

**(2*S*,3*S*)-2-(4-Bromobenzyloxy)-3,4-dihydroxy-3,4-*O*-isopropylidene-*N*-(2-piperidin-1-yl-ethyl)-butyramide (58).** Compound **58** was synthesized in 91% yield from **51** and 1-(2-aminoethyl)-piperidine according to the procedure for preparing **4**. Chromatography eluent: toluene/ethyl acetate 1:1 + 1.5% $Et_3N$. **58**: $[\alpha]_D^{22}$ −34.9 (*c* 1.1, $CHCl_3$); NMR data: See compound **4**. MS calcd for $C_{21}H_{32}BrN_2O_4$ $(M+H)^+$: 455.16. Found: 455.20.

**(2*S*,3*S*)-2-(4-Bromobenzyloxy)-3,4-epoxy-*N*-(2-piperidin-1-yl-ethyl)-butyramide (59).** Compound **59** was synthesized in 87% yield from **58** according to the procedure for preparing **8**. Chromatography eluent: ethyl acetate/MeOH 5:1 + 1% $Et_3N$. **59**: $[\alpha]_D^{22}$ −25.2 (*c* 1.1, $CHCl_3$); NMR data: See compound **8**. MS calcd for $C_{18}H_{26}BrN_2O_3$ $(M+H)^+$: 397.11. Found: 397.11.

**(2*S*,3*S*)-4-(*N*-Benzyl-*N*′-benzyloxycarbonyl-hydrazino)-2-(4-bromobenzyloxy)-3-hydroxy-*N*-(2-piperidin-1-yl-ethyl)-butyramide (60).** Compound **60** was synthesized in 82% yield from **59** and CbzNHNHBn according to the procedure for preparing **32**. Chromatography eluent: ethyl acetate/MeOH 5:1 + 1% $Et_3N$. **60**: $[\alpha]_D^{22}$ −9.9 (*c* 1.0, $CHCl_3$); NMR data: See compound **32**. HRMS calcd for $C_{33}H_{42}BrN_4O_5$ $(M+H)^+$: 653.2338. Found: 653.2333. Purity: 98%.

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## References and Notes

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20. The reaction mixture in this case rapidly turned deeply red, indicating that some sort of side reaction, for example polymerization, was in progress.
21. The standard conditions for protecting a basic nitrogen with a Cbz group, that is using, for example, Z-Cl and $K_2CO_3$ in $THF/H_2O$, proved to be unsuitable here, giving rise to slow reaction rates and low yields of the desired products (mainly due to solubility reasons).
22. Since the target carbamates **42**–**45** did not seem to undergo spontaneous ring-closure even at high temperatures (see the Experimental), we concluded that a probable mechanism for the formation of these molecules is initial carbonate formation at the free hydroxyl position of the free hydrazines, followed by ring-closure to form the six-membered rings.
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