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A Straightforward Approach to MMP-2 and MMP-9 Inhibitors Based on Chelate Claisen Rearrangements

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The chelate Claisen rearrangement is a versatile tool for the stereoselective synthesis of β-substituted γ,δ-unsaturated amino acids, which can be converted into β-substituted aspartates by oxidative cleavage. These are ideal precursors for the synthesis of hydroxamate-type MMP inhibitors.

Introduction

Metastasis, the invasion of tumour cells into distant organs, is often a deadly consequence of tumour growth. It requires the degradation of extracellular matrices by proteolytic enzymes.[1] In addition to serine and cysteine proteases, the matrix metalloproteases (MMPs) in particular play a dominant role.[2] Therefore MMPs are interesting targets for the development of antitumour drugs.[3] This large group of calcium-dependent zinc-containing endopeptidases can be divided into subclasses, for example, collagenases, gelatinases, stromelysines, matrilysines and membrane-type MMPs, depending on their preferred substrates and function. MMP-2 and -9 in particular play a central role in tumour growth and metastasis, whereas other MMPs are involved in arthritis, arteriosclerosis or cardiovascular diseases. In the cellular system, MMPs are regulated by hormones and growth factors and are strictly controlled by endogenous MMP inhibitors (MMPIs) and tissue inhibitors of MMPs (TIMPs).[4] The overexpression of MMPs causes an imbalance in the cell, which leads to a variety of pathological disorders.[5] Therefore the development of efficient selective inhibitors is essential for the treatment of a wide range of diseases.[6]

With respect to cancer treatment, a wide range of inhibitors have been developed during recent decades, most of them belonging to the group of so-called right-hand-side inhibitors with a hydroxamate functionality as the zinc-binding motif. Figure 1 gives an overview of the structure–activity relationship (SAR) of this type of inhibitor.[7] The R^1 substituent mainly determines the activity and the selectivity of the inhibitors. Small substituents are preferred for MMP-1 activity, whereas MMP-2 and MMP-9 with a large binding pocket at this position can be addressed with long R^1 side-chains.

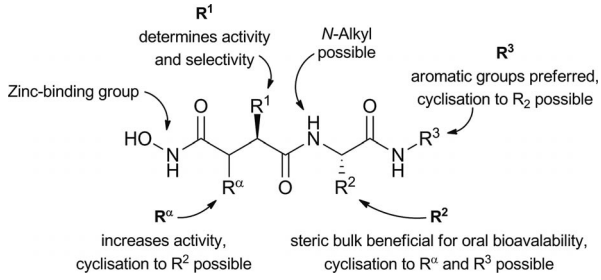

Figure 1. SAR of right-hand side MMP inhibitors.

The introduction of polar side-chains at position R^α often increases the activity, mainly by increasing the solubility of the inhibitors. The substituent R^2 is rather flexible. Aromatic side-chains are preferred for in vitro activity, whereas sterically demanding groups are beneficial for bioavailability by suppressing hydrolysis of the adjacent amide bond. This side-chain can also be connected to substituent R^α and R^3. *N*-Methylations are tolerated on the amide backbone, whereas reverse amide bonds reduce activity.

Two typical examples of inhibitors are shown in Figure 2. Whereas batimastat (**A**) is a highly potent broadband inhibitor,[8] compound **B** with a larger R^1 side-chain interacts selectively with the cancer-relevant MMP-2 and -9, whereas MMP-1 and -3 are much less affected.[1,9] The slightly lower activity of **B** relative to **A** might be the result of the missing R^α substituent.

For some time our group has been involved in the synthesis of unusual amino acids and pharmaceutically important peptides.[10] The key intermediates in our synthetic protocols are chelated amino acid ester enolates. These are excellent nucleophiles in a wide range of reactions, for example, Michael additions[11] and transition-metal-catalysed allylic alkylations.[12] If allylic esters are used, the chelated

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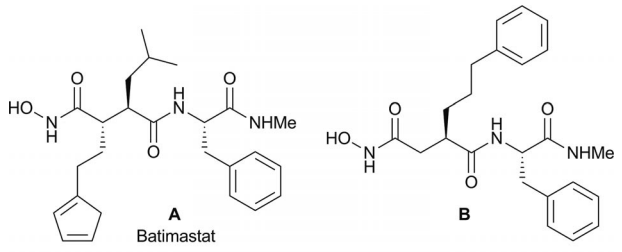


Inhibitor \ IC_{50} [nM]	MMP-1	MMP-2	MMP-3	MMP-8	MMP-9
A	10	4	20	10	1
B	1000	15	500	30	15

Figure 2. MMP inhibition of selected hydroxamate-type inhibitors.

enolates can undergo Claisen rearrangement to give γ,δ-unsaturated amino acids.[13] This approach is not limited to amino acids, but can also be applied to the modification of peptides.[14] Herein, we describe an application of the chelate enolate Claisen rearrangement for the synthesis of MMP inhibitors **1** (Figure 3).

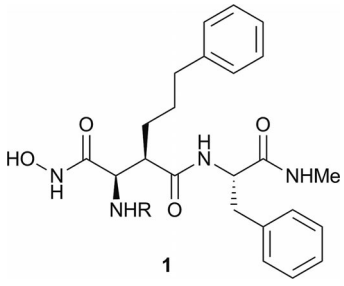
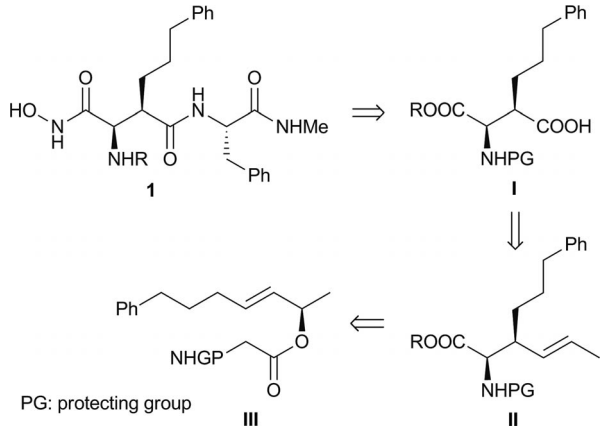


Figure 3. Potential MMP inhibitors **1**.

Results and Discussion

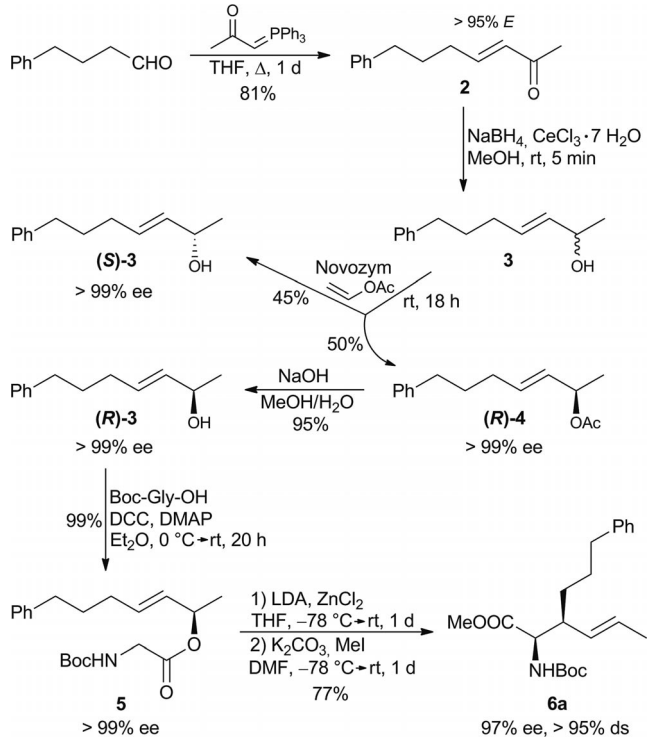
Our retrosynthetic plan is shown in Scheme 1. The hydroxamate functionality should be generated in the last step from a suitable α-amino acid ester **I** after coupling of the phenylalanine amide with the β-carboxylic acid. This functionality should be accessible by oxidative cleavage of the γ,δ-unsaturated acid **II**, which is available by chelate Claisen rearrangement of chiral allylic ester **III**.

Our synthesis started with the preparation of the required chiral allylic alcohol (Scheme 2). Starting from 4-phenylbutyraldehyde, easily accessible from commercial 4-phenylbutanol or butyric acid, the α,β-unsaturated ketone **2** was obtained from a Wittig reaction with excellent *E* selectivity (determined by NMR). Subsequent Luche reduction[15] provided the corresponding allylic alcohol **3** in almost quantitative yield in a few minutes. This allyl alcohol is a perfect substrate for enzymatic kinetic resolution using Novozym 435®.[16] The reaction stopped after 50% conversion giving rise to both enantiomers of the allylic alcohol **3** with >99% *ee*. For our synthesis we required the *R*-configured alcohol (*R*)-**3**, which was obtained from the acetate (*R*)-**4** by saponification. Coupling with Boc-glycine under



Scheme 1. Retrosynthesis of **1**.

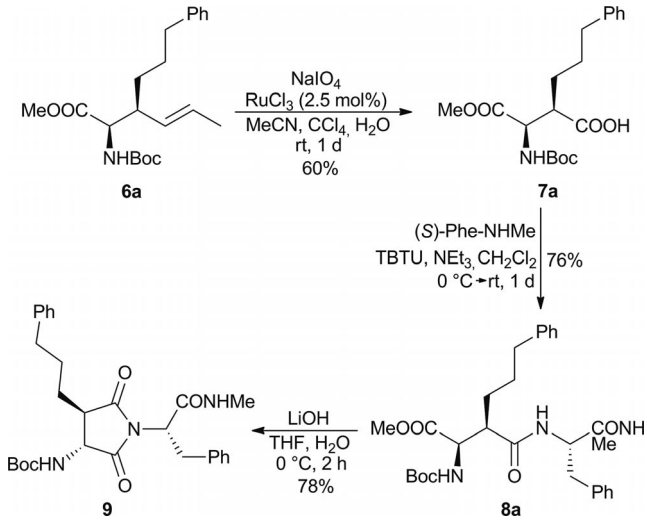
Steglich conditions (DCC, DMAP)[17] provided allyl ester **5** in excellent yield. Subjecting this ester to the typical reaction conditions of the chelate Claisen rearrangement (3 equiv. LDA, 1.2 equiv. $ZnCl_2$) and allowing the reaction mixture to warm overnight to room temperature provided the γ,δ-unsaturated amino acid, which was directly converted into the corresponding methyl ester **6a**.[18]



Scheme 2. Synthesis of γ,δ-unsatutrated amino acid ester **6a**; ds = diastereoselectivity.

In accord with Scheme 3, ester **6a** was subjected to oxidative cleavage with $NaIO_4/RuCl_3$. This reaction has worked well with related substrates without a phenyl ring,[19] but in this case the yield was limited to 60%. Probably the phenyl ring is also attacked during the long reaction.

Reducing the reaction time led to no improvement, in this case the required carboxylic acid **7a** was accompanied by the corresponding aldehyde and diol.

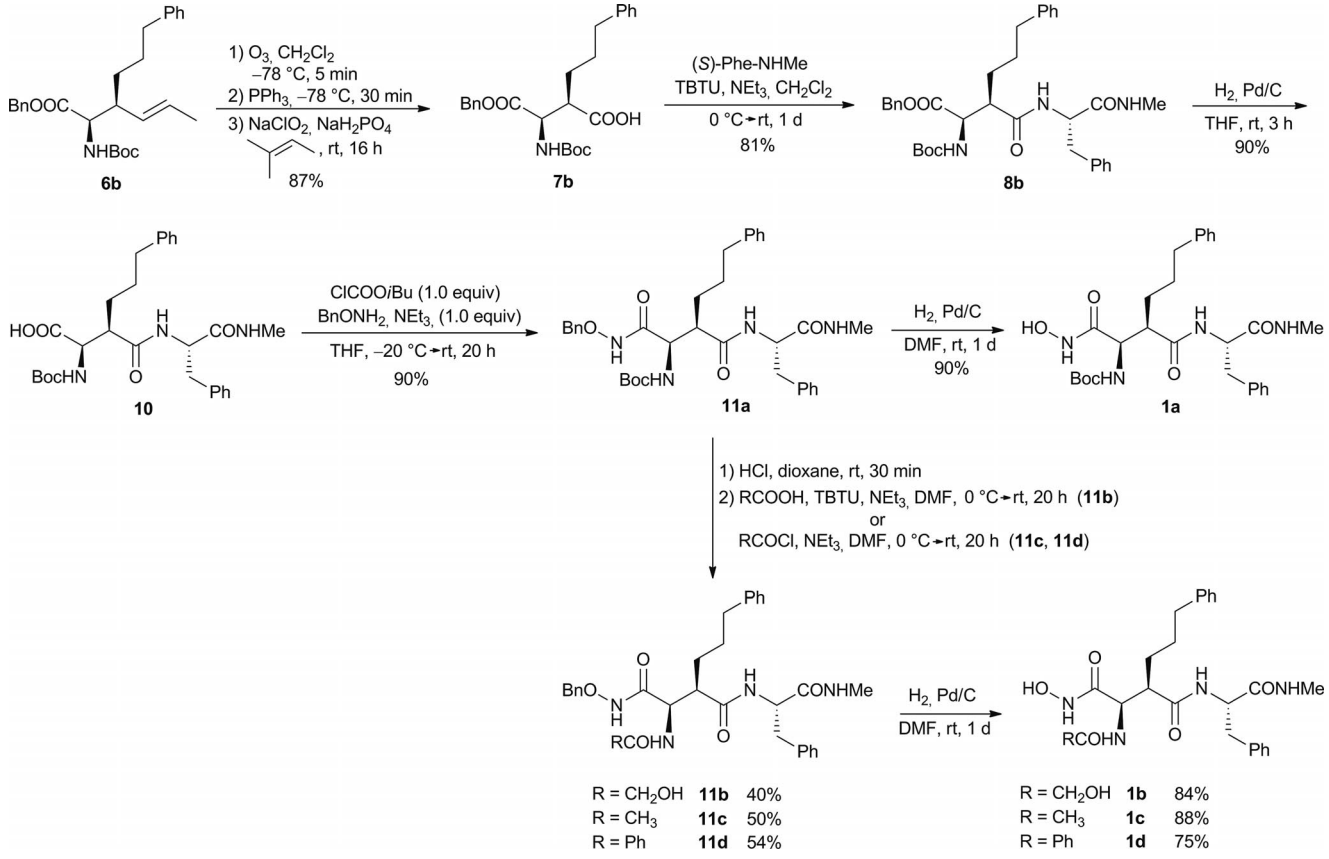


Scheme 3. Formation of succinimide **9**.

Carboxylic acid **7a** was subsequently coupled to the methylamide of (*S*)-phenylalanine to give dipeptide **8a**. At this point, in principle, the methyl ester only has to be converted into the corresponding hydroxamate to finalize the synthesis. But this operation was far from trivial. The attempt to saponify the methyl ester with LiOH (or NaOH) resulted in a very clean reaction (spot to spot on TLC). However, the required carboxylic acid was not formed, but the succinimide **9**.[20] Evidently, under the basic conditions, deprotonation of the amide occurred followed by nucleophilic attack on the methyl ester. Attempts to open the succinimide by using *O*-protected hydroxylamine to give the required *O*-protected hydroxamate were unsuccessful.

Therefore we decided to change our protocol slightly by replacing the methyl ester **6a** with benzyl ester **6b**. This ester was obtained in 93% yield by a similar approach to that described in Scheme 2 simply by alkylating the crude carboxylic acid with benzyl bromide (instead of methyl iodide). Attempts to cleave the ester **6b** directly to give the required carboxylic acid by using the $RuCl_3/NaIO_4$ protocol also failed with this substrate.

Therefore we switched to a two-step protocol starting with ozonolysis to give the corresponding aldehyde followed by oxidation. The ozonolysis of **6b** proceeded without any problems and with PPh_3 as reducing agent the expected aldehyde was obtained in 88% yield after flash chromatography. Interestingly, around 20% epimerization at the β-position of the amino acid ester was observed during chromatography (as determined by NMR). The subsequent oxidation with sodium chlorite gave the required aspartate derivative **7b** in quantitative yield and without further epimerization.[21] Therefore we decided not to perform the purification step and to oxidize the crude aldehyde directly. And indeed, under these conditions the acid **7b** was



Scheme 4. Syntheses of MMP inhibitors **1**.

obtained in enantiomerically pure form in good yield (Scheme 4). Subsequent peptide coupling with (*S*)-Phe-NHMe according to the previous protocol gave rise to the dipeptide **8b** in good yield. Note that the free amine should be used in the coupling step and not the corresponding hydrochloride. In the presence of excess base (to liberate the amine) the desired peptide **8b** was not obtained but the cyclization product **9**.

Benzyl ester **8b** was subjected to catalytic hydrogenation providing the required *N*-protected peptide acid **10** in high yield. The next step, the coupling with the *O*-protected hydroxylamine, was critical because we had to activate the acid without the previously mentioned cyclization taking place. We decided to activate the acid by the mixed anhydride method, with the free *O*-benzylhydroxylamine (not the hydrochloride) and exactly 1 equiv. of NEt_3 to remove the HCl formed. Under these conditions the desired protected hydroxamate **11a** was obtained in high yield without the formation of imide **9**. Unfortunately, this compound is nearly insoluble in most solvents. Therefore we had to perform the final hydrogenation in DMF as solvent. Because of the poor solubility it was nearly impossible to monitor the reaction. After hydrogenation for 1 d the free hydroxamate **1a** was obtained in good yield. This compound was investigated as an inhibitor of the cancer-relevant MMP-2 and -9 (Table 1). Although the activity was not in the low nM range as with the standard inhibitor Batimastat, IC_{50} values in the sub μM range were not disappointing for our first inhibitor molecule with a simple Boc-protecting group. This protecting group was chosen because it can easily be removed, allowing the introduction of a wide range of other substituents at the α position. To increase the polarity and solubility in polar solvents we decided to convert **11a** into the glycolic acid derivative **11b**. TBTU [2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate] was used as the coupling reagent, allowing the removal of the byproducts by diluting the DMF solution with CH_2Cl_2 because **11b** is insoluble in CH_2Cl_2 and can be filtered off easily. The final hydrogenation in DMF gave **1b**.

Table 1. IC_{50} values of MMP inhibitors **1**.

MMP	IC_{50} [μM]			
	1a	**1b**	**1c**	**1d**
MMP-2	0.39	24.7	19,6	16.8
MMP-9	0.15	11.5	6.2	6.2

After removal of the solvent, the crude product was suspended in MeOH and filtered to provide **1b** in pure form. Interestingly, although **1b** seems to be more soluble, the IC_{50} values were significantly worse that those of compound **1a**. Therefore we also replaced the Boc group by other less polar acyl groups, namely the acetyl (**1c**) and benzoyl (**1d**) groups. These derivatives showed comparable activity in the μM range.

Conclusions

We have shown that the chelate enolate Claisen rearrangement is a powerful tool for the synthesis of β-substituted aspartates, which can be used as building blocks for the synthesis of hydroxamate-based MMP inhibitors. The new derivatives **1** showed inhibition of MMP-2 and -9, proteases involved in tumour growth and metastasis, in the low or sub μM range. The major handicap of the new inhibitors is their low solubility in most solvents and probably also under physiological conditions.

Experimental Section

General: All reactions were carried out in oven-dried glassware (70 °C) under nitrogen. Dried solvents were distilled before use: THF was distilled from $LiAlH_4$ and dry DMF was purchased from Sigma–Aldrich. The products were purified by flash chromatography on silica gel columns (Macherey–Nagel 60, 0.063–0.2 mm). Mixtures of ethyl acetate and hexanes were generally used as eluents. Analytical TLC was performed on precoated silica gel plates (Macherey–Nagel, Polygram® SIL G/UV254). Visualization was accomplished with UV light, $KMnO_4$, or ninhydrin solution. The enantiomeric and diastereomeric ratios were determined by HPLC using a chiral column (Trentec, Reprosil 100 Chiral-NR, 250 × 4.6 mm) or by GC (Chirasil–Dex-CB). Optical rotations were measured with a Perkin–Elmer PE 341 polarimeter. ^1H and ^{13}C NMR spectra were recorded with a Bruker AC-400 [400 (^1H) and 100 MHz (^{13}C)] spectrometer in $CDCl_3$, MeOD, or [D_6]DMSO. Chemical shifts are reported in ppm (δ) with respect to TMS and $CHCl_3$ was used as the internal standard. Mass spectra were recorded with a Finnigan MAT 95 spectrometer by using the CI or EI technique. Elemental analyses were performed at Saarland University.

(*E*)-7-Phenylhept-3-en-2-one (2):[22] A solution of 1-(triphenylphosphoranylidene)-2-propanone (10.4 g, 32.5 mmol) and 4-phenylbutyraldehyde (4.68 g, 31.6 mmol) in THF (150 mL) was heated at reflux for 24 h. The reaction mixture was concentrated and diluted with hexanes. The precipitate was filtered off and the filtrate was concentrated again. After purification by flash chromatography (hexanes/ethyl acetate, 9:1) unsaturated ketone **2** (4.95 g, 26.3 mmol, 81%, >95% *E*) was obtained as a colourless oil. TLC: R_f = 0.19 (hexanes/ethyl acetate, 9:1). ^1H NMR ($CDCl_3$): δ = 1.82 (tt, $^3J_{6,5}$ = 7.6, $^3J_{6,7}$ = 7.5 Hz, 2 H, 6-H), 2.23–2.29 (m, 5 H, 7-H, 11-H), 2.66 (t, $^3J_{5,6}$ = 7.6 Hz, 2 H, 5-H), 6.08 (dt, $^3J_{9,8}$ = 16.0, $^4J_{9,7}$ = 1.5 Hz, 1 H, 9-H), 6.80 (dt, $^3J_{8,9}$ = 16.0, $^4J_{8,7}$ = 6.9 Hz, 1 H, 8-H), 7.16–7.21 (m, 3 H, 1-H, 3-H), 7.29 (m, 2 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 26.9 (q, C-11), 29.7 (t, C-6), 31.9 (t, C-7), 35.3 (t, C-5), 126.0 (d, C-1), 128.4 (d, C-2, C-3), 131.5 (d, C-9), 141.6 (s, C-4), 147.9 (d, C-8), 198.6 (s, C-10) ppm. No signals of the *Z* isomer were detected by NMR spectroscopy.

(*E*)-7-Phenylhept-3-en-2-ol (3): Sodium borohydride (0.92 g, 24.4 mmol) was added over 5 min to a solution of **2** (4.59 g, 24.4 mmol) and $CeCl_3 \cdot 7H_2O$ (9.09 g, 24.4 mmol) in MeOH (60 mL). After stirring for an additional 5 min at room temperature, the reaction mixture was quenched with 1 M aqueous $KHSO_4$ and extracted thrice with diethyl ether. The organic layer was washed with brine and concentrated. After purification by flash chromatography (hexanes/ethyl acetate, 8:2) racemic alcohol **3** (4.58 g, 24.1 mmol, 99%) was obtained as a colourless oil. TLC: R_f = 0.21 (hexanes/ethyl acetate 8:2). HPLC (Reprosil, hexanes/*i*PrOH, 98:2, 1 mL/min): (*S*)-**3**: t_R = 9.64 min, (*R*)-**3**: t_R = 10.11 min. ^1H NMR ($CDCl_3$): δ = 1.26 (d, $^3J_{11,10}$ = 6.3 Hz, 3 H, 11-H), 1.41 (br. s, 1 H, OH), 1.72 (tt, $^3J_{6,5}$ = 7.7, $^3J_{6,7}$ = 7.6 Hz, 2 H, 6-H), 2.07 (m, 2 H, 7-H), 2.62 (t, $^3J_{5,6}$ = 7.7 Hz, 2 H, 5-H), 4.26

(m, 1 H, 10-H), 5.53 (ddt, $^3J_{9,8}$ = 15.4, $^3J_{9,10}$ = 6.5, $^4J_{9,7}$ = 1.2 Hz, 1 H, 9-H), 5.65 (dt, $^3J_{8,9}$ = 15.4, $^3J_{8,7}$ = 6.6 Hz, 1 H, 8-H), 7.16–7.20 (m, 3 H, 1-H, 3-H), 7.28 (m, 2 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 23.4 (q, C-11), 30.8 (t, C-6), 31.6 (t, C-7), 35.3 (t, C-5), 68.9 (d, C-10), 125.7 (d, C-1), 128.3, 128.4 (2 d, C-2, C-3), 130.5 (d, C-8), 134.6 (d, C-9), 142.3 (s, C-4) ppm. HRMS (CI): calcd. for $C_{13}H_{18}O$ $[M]^+$ 190.1358; found 190.1363.

(2*S*,*E*)-7-Phenylhept-3-en-2-ol [(*S*)-3]: Novozym 435® (207 mg) was added to a solution of racemic **3** (3.85 g, 20.2 mmol) in vinyl acetate (18.7 mL, 202 mmol). The reaction mixture was shaken at room temperature for 18 h. The enzyme was filtered off and washed with diethyl ether. The combined filtrates were concentrated and the residue was purified by flash chromatography (hexanes/ethyl acetate, 9:1) to give acetate (*R*)-**4** (2.38 g, 10.3 mmol, 50%, >99% *ee*) and alcohol (*S*)-**3** (1.69 g, 8.90 mmol, 45%, >99% *ee*), both as colourless oils. TLC: R_f = 0.32 (hexanes/ethyl acetate, 7:3). HPLC (Reprosil, hexanes/*i*PrOH, 98:2, 1 mL/min): (*S*)-**3**: t_R = 9.64 min; $[\alpha]_D^{20}$ = –9.2 (*c* = 1.1, $CHCl_3$, >99% *ee*). ^{1}H NMR ($CDCl_3$): δ = 1.26 (d, $^3J_{11,10}$ = 6.3 Hz, 3 H, 11-H), 1.41 (br. s, 1 H, OH), 1.72 (tt, $^3J_{6,5}$ = 7.7, $^3J_{6,7}$ = 7.6 Hz, 2 H, 6-H), 2.07 (m, 2 H, 7-H), 2.62 (t, $^3J_{5,6}$ = 7.7 Hz, 2 H, 5-H), 4.26 (m, 1 H, 10-H), 5.53 (ddt, $^3J_{9,8}$ = 15.4, $^3J_{9,10}$ = 6.5, $^4J_{9,7}$ = 1.2 Hz, 1 H, 9-H), 5.65 (dt, $^3J_{8,9}$ = 15.4, $^3J_{8,7}$ = 6.6 Hz, 1 H, 8-H), 7.16–7.20 (m, 3 H, 1-H, 3-H), 7.29 (m, 2 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 23.4 (q, C-11), 30.8 (t, C-6), 31.6 (t, C-7), 35.3 (t, C-5), 68.9 (d, C-10), 125.7 (d, C-1), 128.3, 128.4 (2 d, C-2, C-3), 130.5 (d, C-8), 134.6 (d, C-9), 142.3 (s, C-4) ppm. HRMS (CI): calcd. for $C_{13}H_{18}O$ $[M]^+$ 190.1358; found 190.1363.

(2*R*,*E*)-7-Phenylhept-3-en-2-ol [(*R*)-3]: A 1 M sodium hydroxide solution (12.0 mL, 12.0 mmol) was added to a solution of acetate (*R*)-**4** (2.28 g, 9.80 mol) in methanol (50 mL) at 0 °C. After 30 min the cooling bath was removed and the solution was warmed to room temperature overnight. The reaction mixture was quenched with 1 M $KHSO_4$ solution and extracted with diethyl ether. The combined organic layers were washed with saturated $NaHCO_3$, dried with Na_2SO_4 and concentrated in vacuo. After purification by flash chromatography (hexanes/ethyl acetate, 7:3) alcohol (*R*)-**3** (1.77 g, 9.30 mmol, 95%, >99% *ee*) was obtained as a colourless oil. TLC: R_f = 0.32 (hexanes/ethyl acetate, 7:3). HPLC (Reprosil, hexanes/*i*PrOH, 98:1, 1 mL/min): (*R*)-**3**: t_R = 10.11 min; $[\alpha]_D^{20}$ = +8.5 (*c* = 1.2, $CHCl_3$, >99% *ee*). ^{1}H NMR ($CDCl_3$): δ = 1.26 (d, $^3J_{11,10}$ = 6.3 Hz, 3 H, 11-H), 1.41 (br. s, 1 H, OH), 1.72 (tt, $^3J_{6,5}$ = 7.7, $^3J_{6,7}$ = 7.6 Hz, 2 H, 6-H), 2.07 (m, 2 H, 7-H), 2.62 (t, $^3J_{5,6}$ = 7.7 Hz, 2 H, 5-H), 4.26 (m, 1 H, 10-H), 5.53 (ddt, $^3J_{9,8}$ = 15.4, $^3J_{9,10}$ = 6.5, $^4J_{9,7}$ = 1.2 Hz, 1 H, 9-H), 5.65 (dt, $^3J_{8,9}$ = 15.4, $^3J_{8,7}$ = 6.6 Hz, 1 H, 8-H), 7.16–7.20 (m, 3 H, 1-H, 3-H), 7.29 (m, 2 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 23.4 (q, C-11), 30.8 (t, C-6), 31.6 (t, C-7), 35.3 (t, C-5), 68.9 (d, C-10), 125.7 (d, C-1), 128.3, 128.4 (2 d, C-2, C-3), 130.5 (d, C-8), 134.6 (d, C-9), 142.3 (s, C-4) ppm. HRMS (CI): calcd. for $C_{13}H_{18}O$ $[M]^+$ 190.1358; found 190.1363.

(2*R*,*E*)-7-Phenylhept-3-en-2-yl Acetate [(*R*)-4]: The acetate (*R*)-**4** was obtained together with (*S*)-**3** in the enzymatic kinetic resolution of racemic **3**. TLC: R_f = 0.36 (hexanes/ethyl acetate, 9:1); $[\alpha]_D^{20}$ = +52.1 (*c* = 1.2, $CHCl_3$, >99% *ee*). GC (Chirasil–Dex-CB, 1. 80 °C, 3 min; 2. 4 °C/min; 3. 220 °C, 20 min): (*S*)-**4**: t_R = 35.78 min, (*R*)-**4**: t_R = 36.17 min. ^{1}H NMR ($CDCl_3$): δ = 1.29 (d, $^3J_{11,10}$ = 6.4 Hz, 3 H, 11-H), 1.71 (tt, $^3J_{6,5}$ = 7.7, $^3J_{6,7}$ = 7.6 Hz, 2 H, 6-H), 2.03–2.10 (m, 5 H, 7-H, 13-H), 2.61 (t, $^3J_{5,6}$ = 7.7 Hz, 2 H, 5-H), 5.32 (m, 1 H, 10-H), 5.47 (ddt, $^3J_{9,8}$ = 15.4, $^3J_{9,10}$ = 6.8, $^4J_{9,7}$ = 1.4 Hz, 1 H, 9-H), 5.71 (dt, $^3J_{8,9}$ = 15.4, $^3J_{8,7}$ = 6.8 Hz, 1 H, 8-H), 7.16–7.20 (m, 3 H, 1-H, 3-H), 7.28 (m, 2 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.4 (q, C-13), 21.4 (q, C-11), 30.6 (t, C-6), 31.6 (t, C-7), 35.3 (t, C-5), 71.1 (d, C-10), 125.7 (d, C-1), 128.3, 128.4 (2 d, C-2, C-3), 130.0 (d, C-9), 132.8 (d, C-8), 142.3 (s, C-4), 170.3 (s, C-12) ppm. HRMS (CI): calcd. for $C_{13}H_{16}$ $[M - C_2H_4O_2]^+$ 172.1252; found 172.1255. $C_{15}H_{20}O_2$ (232.32): calcd. C 77.55, H 8.68; found C 77.08, H 8.57.

(2*R*,*E*)-7-Phenylhept-3-en-2-yl 2-(*tert*-Butoxycarbonylamino)acetate (5): A solution of Boc-protected glycine (1.58 g, 9.00 mmol) in diethyl ether (40 mL) was added to a solution of alcohol (*R*)-**3** (1.55 g, 8.20 mmol) in diethyl ether (40 mL) followed by solid DMAP (105 mg, 0.86 mmol). The solution was cooled to 0 °C and a solution of DCC (1.88 g, 9.10 mmol) in diethyl ether (20 mL) was added. The solution was warmed to room temperature overnight and the precipitate was filtered off. The filtrate was washed with 1 M $KHSO_4$ (twice), water, saturated $NaHCO_3$, brine, dried with Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (hexanes/ethyl acetate, 8:2) to yield ester **5** (2.83 g, 8.15 mmol, 99%, >99% *ee*) as a colourless oil. TLC: R_f = 0.31 (hexanes/ethyl acetate, 8:2); $[\alpha]_D^{20}$ = +39.2 (*c* = 0.8, $CHCl_3$, >99% *ee*). HPLC (Reprosil, hexanes/*i*PrOH, 98:2, 1 mL/min): (*R*)-**5**: t_R = 26.52 min, (*S*)-**5**: t_R = 40.20 min. ^{1}H NMR ($CDCl_3$): δ = 1.31 (d, $^3J_{11,10}$ = 6.4 Hz, 3 H, 11-H), 1.45 (s, 3 H, 16-H), 1.71 (tt, $^3J_{6,5}$ = 7.7, $^3J_{6,7}$ = 7.5 Hz, 2 H, 6-H), 2.07 (m, 2 H, 7-H), 2.61 (t, $^3J_{5,6}$ = 7.7 Hz, 2 H, 5-H), 3.88 (m, 2 H, 13-H), 4.99 (br. s, 1 H, NH), 5.38 (m, 1 H, 10-H), 5.46 (ddt, $^3J_{9,8}$ = 15.2, $^3J_{9,10}$ = 6.9, $^4J_{9,7}$ = 1.4 Hz, 1 H, 9-H), 5.73 (dt, $^3J_{8,9}$ = 15.2, $^3J_{8,7}$ = 6.8 Hz, 1 H, 8-H), 7.15–7.19 (m, 3 H, 1-H, 3-H), 7.27 (m, 2 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.3 (q, C-11), 28.3 (q, C-16), 30.5 (t, C-6), 31.6 (t, C-7), 35.3 (t, C-8), 42.7 (t, C-13), 72.5 (d, C-10), 79.9 (s, C-15), 125.7 (d, C-1), 128.3, 128.4 (2 d, C-2, C-3), 129.4 (d, C-9), 133.5 (d, C-8), 142.2 (s, C-4), 155.6 (s, C-14), 169.6 (s, C-12) ppm. HRMS (CI): calcd. for $C_{20}H_{30}NO_4$ $[M + H]^+$ 348.2175; found 348.2192. $C_{20}H_{29}NO_4$ (347.45): calcd. C 69.14, H 8.41, N 4.03; found C 68.95, H 8.30, N 4.09.

Methyl (2*R*,3*S*,*E*)-2-(*tert*-Butoxycarbonylamino)-3-(3-phenylpropyl)-hex-4-enoate (6a): *n*BuLi (1.6 M in hexanes, 12.0 mL, 19.2 mmol) was added dropwise to a solution of diisopropylamine (3.40 mL, 24.1 mmol) in dry THF (24 mL) at –30 °C. The clear solution was warmed to room temperature and then cooled to –78 °C (base solution). In another Schlenk tube, ester **5** (2.70 g, 7.80 mmol) was added to a solution of $ZnCl_2$ (1.28 g, 9.40 mmol) in dry THF (45 mL). This solution was also cooled to –78 °C (substrate solution). The base solution was then slowly added to the substrate solution over 20 min and the resulting solution was warmed to room temperature overnight (20 h). The reaction mixture was diluted with diethyl ether and hydrolysed with 1 M $KHSO_4$. The phases were separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated in vacuo.

The crude acid was dissolved in dry DMF (30 mL) and cooled to 0 °C. K_2CO_3 (1.35 g, 9.80 mmol) was added followed by methyl iodide (1.45 mL, 23.3 mmol). The reaction mixture was warmed to room temperature over 20 h, quenched with water and extracted with ethyl acetate. The combined organic layers were washed with water (three times), 5% Na_2SO_3 and brine, dried with Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (hexanes/ethyl acetate, 8:2) to yield ester **6a** (2.16 g, 5.98 mmol, 77%, 97% *ee*, >95% *ds*) as a colourless oil. TLC: R_f = 0.40 (hexanes/ethyl acetate, 8:2); $[\alpha]_D^{20}$ = –14.8 (*c* = 1.2, $CHCl_3$, 97% *ee*, >95% *ds*). HPLC (Reprosil, hexanes/*i*PrOH, 98:2, 1 mL/min): (2*R*,3*S*)-**6a**: t_R = 11.39 min; (2*S*,3*R*)-**6a**: t_R = 12.66 min. ^{1}H NMR ($CDCl_3$): δ = 1.33 (m, 1 H, 8-H_a), 1.43 (s, 9 H, 6-H), 1.47–1.56 (m,

2 H, 8-H_b, 9-H_a), 1.64 (m, 1 H, 9-H_b), 1.67 (dd, $^3J_{17,16}$ = 6.4, $^4J_{17,15}$ = 1.6 Hz, 3 H, 17-H), 2.30 (m, 1 H, 7-H), 2.59 (m, 2 H, 10-H), 3.68 (s, 3 H, 1-H), 4.23 (dd, $^3J_{3,NH}$ = 8.4, $^3J_{3,7}$ = 6.0 Hz, 1 H, 3-H), 4.98 (d, $^3J_{NH,3}$ = 8.7 Hz, 1 H, NH), 5.12 (ddq, $^2J_{15,16}$ = 15.2, $^3J_{15,7}$ = 9.6, $^4J_{15,17}$ = 1.6 Hz, 1 H, 15-H), 5.50 (dq, $^3J_{16,15}$ = 15.2, $^3J_{16,17}$ = 6.4 Hz, 1 H, 16-H), 7.14–7.19 (m, 3 H, 12-H, 14-H), 7.27 (m, 2 H, 13-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 17.9 (q, C-17), 28.3 (q, C-6), 29.1 (t, C-9), 30.8 (t, C-8), 35.7 (t, C-10), 46.3 (d, C-7), 51.8 (q, C-1), 57.0 (d, C-3), 79.8 (s, C-5), 125.7 (d, C-14), 128.3, 128.4 (2 d, C-12, C-13), 129.0 (d, C-16), 129.5 (d, C-15), 142.3 (s, C-11), 155.3 (s, C-4), 172.4 (s, C-2) ppm. HRMS (CI): calcd. for $C_{21}H_{32}NO_4$ [M + H]$^+$ 362.2331; found 362.2296. $C_{21}H_{31}NO_4$ (361.48): calcd. C 69.78, H 8.64, N 3.87; found C 69.87, H 8.40, N 4.18.

Benzyl (2*R*,3*S*,*E*)-2-(*tert*-Butoxycarbonylamino)-3-(3-phenylpropyl)-hex-4-enoate (6b): In accord with the synthesis of **6a**, diisopropylamine (1.5 mL, 10.6 mmol), *n*BuLi (1.6 M in hexanes, 5.60 mL, 8.96 mmol), ester **5** (1.25 g, 3.60 mmol) and $ZnCl_2$ (605 mg, 4.40 mmol) were allowed to react. After workup, the crude acid was dissolved in dry DMF (20 mL) and cooled to 0 °C. Then Cs_2CO_3 (1.24 g, 3.80 mmol) was added followed by benzyl bromide (0.63 mL, 4.32 mmol). The reaction mixture was warmed to room temperature over 20 h, quenched with water and extracted with ethyl acetate. The combined organic layers were washed with water (three times), 5% Na_2SO_3 and brine, dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (hexanes/ethyl acetate, 9:1) to yield benzyl ester **6b** (1.46 g, 3.30 mmol, 93%, 98% *ee*, >95% *ds*) as a colourless oil. TLC: R_f = 0.23 (hexanes/ethyl acetate, 9:1); $[\alpha]_D^{20}$ = +11.5 (*c* = 1.1, $CHCl_3$, 98% *ee*, >95% *ds*). HPLC (Reprosil, hexanes/*i*PrOH, 98:2, 1 mL/min): (2*R*,3*S*)-**6b**: t_R = 17.17 min; (2*S*,3*R*)-**6b**: t_R = 18.78 min. ^{1}H NMR ($CDCl_3$): δ = 1.26 (m, 1 H, 12-H_a), 1.43 (s, 9 H, 10-H), 1.45–1.53 (m, 2 H, 12-H_b, 13-H_a), 1.62 (m, 1 H, 13-H_b), 1.61 (dd, $^3J_{21,20}$ = 6.4, $^4J_{21,19}$ = 1.5 Hz, 3 H, 21-H), 2.31 (m, 1 H, 11-H), 2.51 (m, 2 H, 14-H), 4.28 (dd, $^3J_{7,11}$ = 8.9, $^3J_{7,NH}$ = 8.8 Hz, 1 H, 7-H), 4.99 (d, $^3J_{NH,7}$ = 8.8 Hz,1 H, NH), 5.05–5.10 (m, 2 H, 5-H_a, 19-H), 5.17 (d, $^3J_{5b,5a}$ = 12.3 Hz, 1 H, 5-H_b), 5.46 (dq, $^3J_{20,19}$ = 15.2, $^3J_{20,21}$ = 6.4 Hz, 1 H, 20-H), 7.11 (d, $^3J_{16,17}$ = 7.0 Hz, 2 H, 16-H), 7.16 (m, 1 H, 18-H), 7.25 (m, 2 H, 17-H), 7.33–7.38 (m, 5 H, 1-H, 2-H, 3-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 17.9 (q, C-21), 28.3 (q, C-10), 29.1 (t, C-13), 30.8 (t, C-12), 35.7 (t, C-14), 46.4 (d, C-11), 57.1 (d, C-7), 66.7 (t, C-5), 79.8 (s, C-9), 125.7 (d, C-18), 128.3, 128.3, 128.4, 128.5 (5 d, C-1, C-2, C-3, C-16, C-17), 129.0 (s, C-20), 129.5 (d, C-19), 135.5 (s, C-4), 142.3 (s, C-15), 155.3 (s, C-8), 171.7 (s, C-6) ppm. HRMS (CI): calcd. for $C_{27}H_{36}NO_4$ [M + H]$^+$ 438.2644; found 438.2597. $C_{27}H_{35}NO_4$ (437.58): calcd. C 74.11, H 8.06, N 3.20; found C 74.00, H 8.05, N 3.58.

(*R*)-2-[(*R*)-1-(*tert*-Butoxycarbonylamino)-2-methoxy-2-oxoethyl]-5-phenylpentanoic Acid (7a): CCl_4 (5 mL) and water (7.5 mL) were added to a solution of **6a** (461 mg, 1.28 mmol) in acetonitrile (5 mL) followed by $RuCl_3 \cdot H_2O$ (35–40%, 18.8 mg, 0.03 mmol) and sodium periodate (1.13 g, 5.28 mmol). The reaction mixture was stirred vigorously for 20 h at room temperature, diluted with water and extracted with dichloromethane. The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. The residue was filtered through silica gel (hexanes/ethyl acetate, 1:1). After evaporating the solvent, the crude acid **7a** (274 mg, 0.75 mmol, 60%) was obtained as an orange resin. This acid was used in the next step without further purification.

(*R*)-2-[(*R*)-2-(Benzyloxy)-1-(*tert*-butoxycarbonylamino)-2-oxoethyl]-5-phenylpentanoic Acid (7b): A solution of olefin **6b** (3.59 g, 8.20 mmol) in dry dichloromethane (80 mL) was cooled to –78 °C and ozone was bubbled through the reaction mixture until a blue colour persisted. After purging the excess of ozone with nitrogen, triphenylphosphane (2.15 g, 8.20 mmol) was added and the solution was warmed to room temperature. Concentration in vacuo gave the crude aldehyde as a colourless oil. The aldehyde was dissolved in *tert*-butyl alcohol (170 mL) before 2-methyl-2-butene (17.6 mL, 164 mmol) was added followed by a solution of $NaClO_2$ (80%, 9.27 g, 82.0 mmol) and $NaH_2PO_4 \cdot 2H_2O$ (8.95 g, 57.4 mmol) in water (60 mL). The yellow emulsion was stirred for 16 h at room temperature. The *tert*-butyl alcohol was removed in vacuo, the residue was acidified with 1 M HCl (pH = 1) and extracted 3× with diethyl ether (50 mL each). The combined organic layers were dried with Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (hexanes/ethyl acetate/acetic acid, 70:29:1) to yield acid **7b** (3.34 g, 7.60 mmol, 93% over two steps) as a colourless resin. TLC: R_f = 0.28 (hexanes/ethyl acetate/acetic acid, 70:29:1); $[\alpha]_D^{20}$ = –4.1 (*c* = 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.32 (s, 9 H, 10-H), 1.54 (m, 1 H, 12-H_a), 1.61 (m, 1 H, 13-H_a), 1.72 (m, 1 H, 13-H_b), 1.82 (m, 1 H, 12-H_b), 2.55 (t, $^3J_{14,13}$ = 7.6 Hz, 2 H, 14-H), 2.89 (m, 1 H, 11-H), 4.68 (m, 1 H, 7-H), 5.13 (d, $^2J_{5a,5b}$ = 12.2 Hz, 1 H, 5-H_a), 5.19 (d, $^2J_{5b,5a}$ = 12.2 Hz, 1 H, 5-H_b), 5.33 (d, $^3J_{NH,7}$ = 8.2 Hz, 1 H, NH), 7.11 (m, 2 H, 16-H), 7.19 (m, 1 H, 18-H), 7.26 (m, 2 H, 17-H), 7.30–7.37 (m, 5 H, 1-H, 2-H, 3-H), 8.50 (br. s, 1 H, OH) ppm. ^{13}C NMR ($CDCl_3$): δ = 27.5 (t, C-12), 28.1 (q, C-10), 29.1 (t, C-13), 35.5 (t, C-14), 47.9 (d, C-11), 54.3 (d, C-7), 67.4 (t, C-5), 80.3 (s, C-9), 125.7 (d, C-18), 128.2, 128.3, 128.4, 128.5 (5 d, C-1, C-2, C-3, C-16, C-17), 135.0 (s, C-4), 141.6 (s, C-15), 155.2 (s, C-8), 170.4 (s, C-6), 177.8 (s, C-19) ppm. HRMS (CI): calcd. for $C_{25}H_{32}NO_6$ [M + H]$^+$ 442.2229; found 442.2231. $C_{25}H_{31}NO_6$ (441.52): calcd. C 68.01, H 7.08, N 3.17; found C 67.58, H 7.07, N 3.30.

***N*-Methyl-(*R*)-2-[(*R*)-2-(methyloxy)-1-(*tert*-butoxycarbonylamino)-2-oxoethyl]-5-phenylpentanoyl-(*S*)-phenylalanineamide (8a):** NEt_3 (0.21 mL, 1.53 mmol) was added to a solution of crude acid **7a** (397 mg, 1.09 mmol), (*S*)-Phe-NHMe (232 mg, 1.30 mmol) and TBTU (357 mg, 1.11 mmol) in dry dichloromethane (10 mL) at 0 °C. The reaction mixture was warmed to room temperature over 18 h. The resulting suspension was diluted with dichloromethane and washed with water (twice), 1 M $KHSO_4$, saturated $NaHCO_3$, water and brine, dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (dichloromethane/methanol, 98:2) to yield peptide **8a** (436 mg, 0.83 mmol, 76%, >95% *ds*) as a white solid; m.p. 189–190 °C. TLC: R_f = 0.51 (dichloromethane/methanol, 95:5); $[\alpha]_D^{20}$ = –21.6 (*c* = 0.9, $CHCl_3$, >95% *ds*). ^{1}H NMR ($CDCl_3$): δ = 1.42 (s, 9 H, 6-H), 1.47–1.66 (m, 4 H, 8-H, 9-H), 2.55 (t, $^3J_{10,9}$ = 7.0 Hz, 2 H, 10-H), 2.65 (br. s, 1 H, 7-H), 2.68 (d, $^3J_{18,NH}$ = 4.8 Hz, 3 H, 18-H), 3.07 (m, 2 H, 19-H), 3.67 (s, 3 H, 1-H), 4.48 (br. s, 1 H, 3-H), 4.57 (m, 1 H, 16-H), 5.34 (d, $^3J_{NH,3}$ = 7.4 Hz, 1 H, NH), 6.02 (br. s, 1 H, NH), 6.29 (d, $^3J_{NH,16}$ = 5.6 Hz, 1 H, NH), 7.10–7.12 (m, 2 H, Ar-H), 7.15–7.20 (m, 3 H, Ar-H), 7.21–7.30 (m, 5 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 26.1 (q, C-18), 28.1 (t, C-9), 28.2 (q, C-6), 28.8 (t, C-8), 35.5 (t, C-10), 38.0 (t, C-19), 49.5 (d, C-7), 52.5 (s, C-1), 54.7 (d, C-16), 54.8 (d, C-3), 80.4 (s, C-5), 125.9, 127.0 (2 d, C-14, C-23), 128.3, 128.7, 129.1 (4 d, C-12, C-13, C-21, C-22), 136.7 (s, C-20), 141.5 (s, C-11), 155.4 (s, C-4), 171.0, 171.5, 171.9 (3 s, C-2, C-15, C-17) ppm. No signals of the *S*,*S*,*S* diastereomer were detected by NMR spectroscopy. HRMS (CI): calcd. for $C_{29}H_{40}N_3O_6$ [M + H]$^+$ 526.2917; found 526.2971. $C_{29}H_{39}N_3O_6$ (525.65): calcd. C 66.27, H 7.48, N 7.99; found C 66.00, H 7.45, N 7.93.

***N*-Methyl-(*R*)-2-[(*R*)-2-(benzyloxy)-1-(*tert*-butoxycarbonylamino)-2-oxoethyl]-5-phenylpentanoyl-(*S*)-phenylalanineamide (8b):** NEt_3 (0.25 mL, 1.81 mmol) was added to a solution of acid **7b** (800 mg,

1.81 mmol), (*S*)-Phe-NHMe (387 mg, 2.17 mmol) and TBTU (581 mg, 1.81 mmol) in dry dichloromethane (20 mL) at 0 °C. The reaction mixture was warmed to room temperature over 18 h. The resulting suspension was diluted with dichloromethane and washed with water (twice), 1 M $KHSO_4$, saturated $NaHCO_3$, water and brine, dried with Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (dichloromethane/methanol, 98:2) to yield peptide **8b** (900 mg, 1.50 mmol, 81%, >95% *ds*) as a white solid; m.p. 189–192 °C. TLC: R_f = 0.27 (dichloromethane/methanol, 98:2); $[\alpha]_D^{20}$ = –8.4 (*c* = 1.0, $CHCl_3$, >95% *ds*). ^{1}H NMR ($CDCl_3$): δ = 1.40 (s, 9 H, 10-H), 1.43–1.49 (m, 3 H, 12-H_a, 13-H), 1.60 (m, 1 H, 12-H_b), 2.45 (t, $^3J_{14,13}$ = 7.1 Hz, 2 H, 14-H), 2.65 (m, 3 H, 11-H), 2.68 (d, $^3J_{22,NH}$ = 4.8 Hz, 3 H, 22-H), 3.03 (m, 2 H, 23-H), 4.48 (br. s, 1 H, 7-H), 4.52 (m, 1 H, 20-H), 5.11 (d, $^2J_{5a,5b}$ = 12.2 Hz, 1 H, 5-H_a), 5.17 (d, $^2J_{5b,5a}$ = 12.2 Hz, 1 H, 5-H_b), 5.37 (d, $^3J_{NH,7}$ = 7.2 Hz, 1 H, NH), 5.92 (br. s, 1 H, NH), 6.14 (d, $^3J_{NH,20}$ = 7.2 Hz, 1 H, NH), 7.06 (d, $^3J_{16,17}$ = 7.0 Hz, 2 H, 16-H), 7.12–7.23 (m, 3 H, 18-H, 25-H), 7.25–7.30 (m, 5 H, 17-H, 26-H, 27-H), 7.32–7.37 (m, 5 H, 1-H, 2-H, 3-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 26.1 (q, C-22), 28.0 (t, C-12), 28.2 (q, C-10), 28.9 (t, C-13), 35.5 (t, C-14), 38.0 (t, C-23), 49.3 (d, C-11), 54.7 (d, C-20), 54.8 (d, C-7), 67.5 (t, C-5), 80.4 (s, C-9), 125.9 (d, C-18), 127.0 (d, C-27), 128.3, 128.3, 128.5, 128.5, 128.6, 128.7, 129.1 (7 d, C-1, C-2, C-3, C-16, C-17, C-25, C-26), 135.1 (s, C-4), 136.7 (s, C-24), 141.5 (s, C-15), 155.4 (s, C-8), 170.9 (2 s, C-19, C-21), 171.8 (s, C-6) ppm. No signals of the *S*,*S*,*S* diastereomer were detected by NMR spectroscopy. HRMS (CI): calcd. for $C_{35}H_{44}N_3O_6$ $[M + H]^+$ 602.3231; found 602.3241. $C_{35}H_{43}N_3O_6$ (601.74): calcd. C 69.86, H 7.20, N 6.98; found C 69.89, H 7.21, N 6.96.

***tert*-Butyl (3*R*,4*R*)-1-[(*S*)-1-(Methylamino)-1-oxo-3-phenylpropan-2-yl]-2,5-dioxo-4-(3-phenylpropyl)pyrrolidin-3-ylcarbamate (9):** A LiOH solution (1 M, 0.19 mL, 0.19 mmol) was added dropwise to a solution of peptide **8a** (94.0 mg, 0.18 mmol) in THF (5 mL) at 0 °C. After stirring for 2 h at this temperature, the reaction mixture was quenched with 1 M $KHSO_4$ (5 mL) and extracted with ethyl acetate. The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated in vacuo. After purification by flash chromatography (hexanes/ethyl acetate, 1:1) imide **9** (70.1 mg, 0.14 mmol, 78%) was obtained as a colourless solid; m.p. 174–175 °C. TLC: R_f = 0.29 (hexanes/ethyl acetate, 1:1). ^{1}H NMR ($CDCl_3$): δ = 1.12–1.31 (m, 3 H, 9-H, 8-H_a), 1.41–1.49 (m, 10 H, 1-H, 8-H_b), 2.46 (t, $^3J_{10,9}$ = 7.0 Hz, 2 H, 10-H), 2.76–2.80 (m, 4 H, 7-H, 17-H), 3.20 (dd, $^3J_{4,NH}$ = 7.0, $^3J_{4,7}$ = 4.9 Hz, 1 H, 4-H), 3.40 (dd, $^2J_{18a,18b}$ = 14.2, $^3J_{18a,15}$ = 12.6 Hz, 1 H, 18-H_a), 3.66 (dd, $^2J_{18b,18a}$ = 14.2, $^3J_{18b,15}$ = 5.0 Hz, 1 H, 18-H_b), 5.03 (dd, $^3J_{15,18a}$ = 12.6, $^3J_{15,18b}$ = 5.0 Hz, 1 H, 15-H), 5.44 (d, $^3J_{NH,4}$ = 6.6 Hz, 1 H, NH), 6.95–7.13 (m, 8 H, Ar-H, NH), 7.19–7.31 (m, 3 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 26.4 (q, C-17), 27.3 (t, C-9), 28.2 (q, C-1), 28.7 (t, C-8), 33.3 (t, C-18), 35.5 (t, C-10), 46.4 (d, C-7), 54.9 (d, C-4), 55.4 (d, C-15), 82.0 (s, C-2), 126.1, 126.7, (2 d, C-14, C-22), 128.4, 128.8, (2 d, C-12, C-13, C-20, C-21), 137.2 (s, C-19), 141.2 (s, C-11), 155.9 (s, C-3), 168.1, 174.5, 176.1 (3 s, C-5, C-6, C-16) ppm. HRMS (CI): calcd. for $C_{28}H_{36}N_3O_5$ $[M + H]^+$ 494.2655; found 494.2650.

(2*R*,3*R*)-2-(*tert*-Butoxycarbonylamino)-3-[(*S*)-1-(methylamino)-1-oxo-3-phenylpropan-2-ylcarbamoyl]-6-phenylhexanoic Acid (10): A solution of peptide **8b** (208 mg, 0.35 mmol) in dry THF (5 mL) was hydrogenated with Pd/C (10%, 23 mg) until TLC showed completion of the reaction. The Pd/C was filtered off and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography (ethyl acetate/acetic acid, 99:1) to yield acid **10** (160 mg, 0.31 mmol, 90%) as a white solid; m.p. 171–173 °C. TLC: R_f = 0.35 (ethyl acetate/acetic acid, 99:1); $[\alpha]_D^{20}$ = +3.1 (*c* = 0.7, MeOH). ^{1}H NMR (MeOD): δ = 1.39–1.49 (m, 11 H, 5-H, 8-H), 1.56 (m, 2 H, 7-H), 2.50 (t, $^3J_{9,8}$ = 7.4 Hz, 2 H, 9-H), 2.61 (s, 3 H, 22-H), 2.72 (m, 1 H, 6-H), 2.98 (dd, $^2J_{16a,16b}$ = 13.7, $^3J_{16a,15}$ = 7.7 Hz, 1 H, 16-H_a), 3.12 (dd, $^2J_{16b,16a}$ = 13.7, $^3J_{16b,15}$ = 7.3 Hz, 1 H, 16-H_b), 4.35 (d, $^3J_{2,6}$ = 8.4 Hz, 1 H, 2-H), 4.50 (dd, $^3J_{15,16a}$ = $^3J_{15,16b}$ = 7.5 Hz, 1 H, 15-H), 7.10–7.12 (m, 3 H, 11-H, 13-H), 7.16 (m, 1 H, 20-H), 7.20–7.27 (m, 6 H, 12-H, 18-H, 19-H) ppm. ^{13}C NMR (MeOD): δ = 26.3 (q, C-22), 28.8 (q, C-5), 29.7, 29.8 (2 t, C-7, C-8), 36.7 (t, C-9), 38.7 (t, C-16), 49.6 (d, C-6), 56.4 (d, C-2), 56.6 (d, C-15), 80.7 (s, C-4), 126.8 (d, C-13), 127.8 (d, C-20), 129.3, 129.5, 130.2 (4 d, C-11, C-12, C-18, C-19), 138.7 (s, C-17), 143.4 (s, C-10), 157.9 (s, C-3), 173.4 (s, C-22), 174.6 (s, C-14), 175.1 (s, C-1) ppm. HRMS (CI): calcd. for $C_{28}H_{36}N_3O_5$ $[M – OH]^+$ 494.2655; found 494.2643. $C_{28}H_{37}N_3O_6$ (511.61): calcd. C 65.73, H 7.29, N 8.21; found C 65.63, H 7.36, N 7.59.

***N*-Methyl-(*R*)-2-[(*R*)-2-(benzyloxyamino)-1-(*tert*-butoxycarbonylamino)-2-oxoethyl]-5-phenylpentanoyl-(*S*)-phenylalanineamide (11a):** *N*-Methylmorpholine (56 μL, 0.53 mmol) and isobutyl chloroformate (71 μL, 0.53 mmol) were added to a solution of acid **10** (267 mg, 0.52 mmol) in dry THF (25 mL) at –20 °C. After 20 min, *O*-benzylhydroxylamine (172 mg, 1.38 mmol) was added dropwise and the reaction mixture was warmed to room temperature (18 h). The solvent was removed in vacuo and the residue was washed with dichloromethane and diethyl ether to yield **11a** (290 mg, 0.47 mmol, 90%) as a white solid; m.p. 216–218 °C. TLC: R_f = 0.27 (dichloromethane/methanol, 98:2); $[\alpha]_D^{20}$ = +3.6 (*c* = 1.0, DMF). ^{1}H NMR ([D$_6$]DMSO): δ = 1.30–1.43 (m, 13 H, 13-H, 10-H, 12-H), 2.42 (m, 2 H, 14-H), 2.52–2.61 (m, 4 H, 11-H, 22-H), 2.85 (dd, $^3J_{23a,23b}$ = 7.6, $^2J_{23a,20}$ = 6.0 Hz, 1 H, 23-H_a), 2.95 (dd, $^3J_{23b,23a}$ = 7.6, $^2J_{23b,20}$ = 6.0 Hz, 1 H, 23-H_b), 4.11 (dd, $^3J_{7,11}$ = 9.0, $^3J_{7,NH}$ = 9.0 Hz, 1 H, 7-H), 4.39 (m, 1 H, 20-H), 4.62 (d, $^2J_{5a,5b}$ = 10.6 Hz, 1 H, 5-H_a), 4.70 (d, $^2J_{5b,5a}$ = 10.6 Hz, 1 H, 5-H_b), 6.88 (d, $^3J_{NH,7}$ = 9.0 Hz, 1 H, NH), 7.08–7.25 (m, 10 H, 16-H, 17-H, 18-H, 25-H, 26-H, 27-H), 7.34–7.36 (m, 5 H, 1-H, 2-H, 3-H), 7.85 (br. s, 1 H, NH), 8.12 (d, $^3J_{NH,20}$ = 7.9 Hz, 1 H, NH), 11.10 (s, 1 H, NH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 25.5 (q, C-22), 27.9 (t, C-12), 28.1 (t, C-13), 28.2 (q, C-10), 35.2 (t, C-14), 37.3 (t, C-23), 47.5 (d, C-11), 53.4 (d, C-7), 54.3 (d, C-20), 76.9 (t, C-5), 78.3 (s, C-9), 125.6 (d, C-18), 126.2 (d, C-27), 128.1, 128.2, 128.2, 128.3 (5 d, C-1, C-16, C-17, C-25, C-26), 128.8, 129.0 (2 d, C-2, C-3), 135.8 (s, C-4), 137.9 (s, C-24), 142.1 (s, C-15), 155.2 (s, C-8), 167.7 (s, C-6), 171.3, 171.8 (2 s, C-19, C-21) ppm. HRMS (CI): calcd. for $C_{28}H_{36}N_3O_5$ $[M – C_7H_8NO]^+$ 494.2655; found 494.2660. $C_{35}H_{44}N_4O_6$ (616.74): calcd. C 68.16, H 7.19, N 9.08; found C 67.61, H 7.17, N 8.94.

***N*-Methyl-(*R*)-2-[(*R*)-2-(benzyloxyamino)-1-(2-hydroxyacetylamino)-2-oxoethyl]-5-phenylpentanoyl-(*S*)-phenylalanineamide (11b):** HCl in dioxane (4 M, 300 μL, 1.20 mmol) was added to **11a** (41 mg, 66 μmol) at room temperature and the reaction mixture was stirred for 30 min before it was concentrated in vacuo. The residue was dissolved in dry DMF (2 mL) and glycolic acid (7 mg, 92 μmol) and TBTU (28 mg, 87 μmol) were added. After cooling to 0 °C, NEt_3 (26 μL, 180 μmol) was added and the reaction mixture was warmed to room temperature overnight. The solvent was removed in vacuo and the residue was washed with dichloromethane to yield **11b** (15 mg, 26 μmol, 40%) as a white solid; m.p. 215–218 °C (dec.); $[\alpha]_D^{20}$ = +2.1 (*c* = 0.5, DMF). ^{1}H NMR ([D$_6$]DMSO): δ = 1.29–1.52 (m, 4 H, 11-H, 12-H), 2.41 (m, 2 H, 13-H), 2.60 (m, 3 H, 26-H), 2.64 (m, 1 H, 10-H), 2.85 (dd, $^2J_{20a,20b}$ = 13.2, $^3J_{20a,19}$ = 7.8 Hz, 1 H, 20-H_a), 2.97 (dd, $^2J_{20b,20a}$ = 13.3, $^3J_{20b,19}$ = 6.2 Hz, 1 H, 20-H_b), 3.83 (d, $^3J_{9,OH}$ = 4.6 Hz, 2 H, 9-H), 4.42–4.49 (m, 2 H, 7-H, 19-H), 4.66 (d, $^2J_{5a,5b}$ = 10.6 Hz, 1 H, 5-H_a), 4.71 (d, $^2J_{5b,5a}$ = 10.6 Hz, 1 H, 5-H_b), 5.54 (br. s, 1 H, OH), 7.10–7.26 (m, 10 H, 15-H, 16-H, 17-H, 22-H, 23-H, 24-H), 7.32–7.40 (m, 5 H, 1-H, 2-H,

3-H), 7.62 (d, $^3J_{NH,7}$ = 8.6 Hz, 1 H, NH), 7.83 (br. s, 1 H, NH), 8.14 (d, $^3J_{NH,19}$ = 7.5 Hz, 1 H, NH), 11.22 (br. s, 1 H, NH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 25.4 (q, C-26), 27.4 (t, C-11), 28.1 (t, C-12), 35.0 (t, C-13), 37.3 (t, C-20), 47.6 (d, C-10), 51.2 (d, C-7), 54.1 (d, C-19), 61.1 (t, C-9), 76.8 (t, C-5), 125.5 (d, C-17), 126.1 (d, C-24), 128.0, 128.1, 128.2, 128.3 (5 d, C-1, C-15, C-16, C-22, C-23), 128.8, 128.9 (2 d, C-2, C-3), 135.6 (s, C-4), 137.8 (s, C-21), 141.9 (s, C-14), 166.9 (s, C-6), 171.0, 171.3, 171.5 (3 s, C-8, C-18, C-25) ppm. HRMS (CI): calcd. for $C_{25}H_{30}N_3O_5$ [M – C_7H_8NO]$^+$ 452.2186; found 452.2185.

***N*-Methyl-(*R*)-2-[(*R*)-2-(benzyloxyamino)-1-(acetylamino)-2-oxoethyl]-5-phenylpentanoyl-(*S*)-phenylalanineamide (11c):** HCl in dioxane (4 M, 1.0 mL, 4.0 mmol) was added to **11a** (97 mg, 0.16 mmol) at room temperature and the reaction mixture was stirred for 30 min before it was concentrated in vacuo. The residue was stirred in dry DMF (3 mL) at 0 °C and NEt_3 (53 μL, 0.38 mmol) was added followed by acetyl chloride (13 μL, 0.18 mmol). The reaction mixture was stirred overnight at room temperature. The solvent was removed in vacuo and the residue was washed with dichloromethane to yield **11c** (44 mg, 79 μmol, 50%) as a white solid; m.p. 234–235 °C; $[\alpha]_D^{20}$ = +24.2 (*c* = 0.8, DMSO). ^{1}H NMR ([D$_6$]DMSO): δ = 1.23–1.27 (m, 4 H, 11-H, 12-H), 1.82 (s, 3 H, 9-H), 2.34–2.56 (m, 5 H, 13-H, 21-H), 2.60 (m, 1 H, 10-H), 2.84 (dd, $^2J_{22a,22b}$ = 13.7, $^3J_{22a,19}$ = 7.8 Hz, 1 H, 22-H$_a$), 2.92 (dd, $^2J_{22b,22a}$ = 13.4, $^3J_{22b,19}$ = 6.1 Hz, 1 H, 22-H$_b$), 4.26–4.47 (m, 2 H, 7-H, 19-H), 4.64 (d, $^2J_{5a,5b}$ = 10.6 Hz, 1 H, 5-H$_a$), 4.69 (d, $^2J_{5b,5a}$ = 10.6 Hz, 1 H, 5-H$_b$), 7.08–7.25 (m, 10 H, 15-H, 16-H, 17-H, 24-H, 25-H, 26-H), 7.35 (br. s, 5 H, 1-H, 2-H, 3-H), 7.80 (q, $^3J_{NH,21}$ = 4.0 Hz, 1 H, NH), 8.01 (d, $^3J_{NH,7}$ = 8.9 Hz, 1 H, NH), 8.13 (d, $^3J_{NH,19}$ = 7.7 Hz, 1 H, NH), 11.10 (s, 1 H, NH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 22.4 (q, C-9), 25.4 (q, C-21), 27.8 (t, C-11), 28.1 (t, C-12), 35.0 (t, C-13), 37.3 (t, C-22), 47.3 (d, C-10), 51.4 (d, C-7), 54.1 (d, C-19), 76.7 (t, C-5), 125.5 (d, C-17), 126.1 (d, C-26), 128.0, 128.1, 128.2, 128.7, 128.9 (7 d, C-1, C-2, C-3, C-15, C-16, C-24, C-25), 125.7 (s, C-4), 137.8 (s, C-23), 142.0 (s, C-14), 167.4 (s, C-6), 169.2 (s, C-8), 171.1, 171.6 (2 s, C-18, C-20) ppm. HRMS (CI): calcd. for $C_{24}H_{30}N_3O_3$ [M – $C_8H_8NO_2$]$^+$ 408.2287; found 408.2270.

***N*-Methyl-(*R*)-2-[(*R*)-2-(benzyloxyamino)-1-(benzoylamino)-2-oxoethyl]-5-phenylpentanoyl-(*S*)-phenylalanineamide (11d):** HCl in dioxane (4 M, 2.0 mL, 8.0 mmol) was added to **11a** (150 mg, 0.24 mmol) at room temperature and the reaction mixture was stirred for 30 min before it was concentrated in vacuo. The residue was stirred in dry DMF (4 mL) at 0 °C and NEt_3 (82 μL, 0.59 mmol) was added followed by benzoyl chloride (33 μL, 0.28 mmol). The reaction mixture was stirred overnight at room temperature. The solvent was removed in vacuo and the residue was washed with dichloromethane to yield **11d** (82 mg, 0.13 mmol, 54%) as a white solid; m.p. 241–242 °C; $[\alpha]_D^{20}$ = +14.8 (*c* = 1.1, DMSO). ^{1}H NMR ([D$_6$]DMSO): δ = 1.30 (m, 2 H, 15-H), 1.47 (m, 2 H, 14-H), 2.40 (m, 2 H, 16-H), 2.54 (d, $^3J_{24,NH}$ = 4.4 Hz, 3 H, 24-H), 2.82 (m, 1 H, 13-H), 2.88 (dd, $^2J_{25a,25b}$ = 13.8, $^3J_{25,22}$ = 8.4 Hz, 1 H, 25-H$_a$), 2.88 (dd, $^2J_{25a,25b}$ = 13.8, $^3J_{25b,22}$ = 8.4 Hz, 1 H, 25-H$_a$), 3.01 (dd, $^2J_{25b,25a}$ = 13.7, $^3J_{25a,22}$ = 5.8 Hz, 1 H, 25-H$_b$), 4.42 (m, 1 H, 22-H), 4.65–4.72 (m, 3 H, 5-H, 7-H), 7.05–7.19 (m, 10 H, 18-H, 19-H, 20-H, 27-H, 28-H, 29-H), 7.31–7.38 (m, 5 H, 1-H, 2-H, 3-H), 7.46 (m, 2 H, 11-H), 7.54 (m, 1 H, 12-H), 7.82 (d, $^3J_{10,11}$ = 7.3 Hz, 1 H, 10-H), 7.88 (q, $^3J_{NH,24}$ = 4.5 Hz, 1 H, NH), 8.22 (d, $^3J_{NH,22}$ = 7.8 Hz, 1 H, NH), 8.46 (d, $^3J_{NH,7}$ = 8.5 Hz, 1 H, NH), 11.14 (s, 1 H, NH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 25.5 (q, C-24), 27.8 (t, C-15), 28.1 (t, C-14), 35.0 (t, C-16), 37.1 (t, C-25), 47.0 (d, C-13), 52.4 (d, C-7), 54.3 (d, C-22), 76.8 (t, C-5), 125.5 (d, C-20), 126.1 (d, C-29), 127.5 (d, C-10), 128.1, 128.2, 128.8, 128.9 (8 d, C-1, C-2, C-3, C-11, C-18, C-19, C-27, C-28), 133.9 (s, C-9), 135.7 (s, C-4), 137.9 (s, C-26), 141.9 (s, C-17), 166.4 (s, C-8), 167.4 (s, C-6), 171.3, 171.9 (2 s, C-21, C-23) ppm. HRMS (CI): calcd. for $C_{29}H_{32}N_3O_3$ [M – C_8H_9NO]$^+$ 470.2444; found 470.2451.

***N*-Methyl-(*R*)-2-[(*R*)-2-(hydroxyamino)-1-(*tert*-butoxycarbonylamino)-2-oxoethyl]-5-phenylpentanoyl-(*S*)-phenylalanineamide (1a):** A solution of **11a** (150 mg, 0.24 mmol) in dry DMF (2 mL) was hydrogenated with Pd/C (10%, 25 mg) until TLC showed completion of the reaction. The Pd/C was filtered off and the filtrate was concentrated in vacuo. The crude product was washed with methanol and diethyl ether to yield hydroxamic acid **1a** (105 mg, 0.20 mmol, 90%) as a white solid; m.p. 245–247 °C; $[\alpha]_D^{20}$ = –5.8 (*c* = 0.5, DMF). ^{1}H NMR ([D$_6$]DMSO): δ = 1.21–1.52 (m, 13 H, 5-H, 7-H, 8-H), 2.40 (m, 2 H, 9-H), 2.52–2.60 (m, 4 H, 6-H, 22-H), 2.86 (dd, $^2J_{16a,16b}$ = 13.6, $^3J_{16a,15}$ = 7.9 Hz, 1 H, 16-H$_a$), 2.99 (dd, $^2J_{16b,16a}$ = 13.7, $^3J_{16b,15}$ = 6.2 Hz, 1 H, 16-H$_b$), 4.14 (dd, $^3J_{2,6}$ = $^3J_{2,NH}$ = 8.6 Hz, 1 H, 2-H), 4.37 (m, 1 H, 15-H), 6.76 (d, $^3J_{NH,2}$ = 8.8 Hz, 1 H, NH), 7.08–7.20 (m, 10 H, 11-H, 12-H, 13-H, 18-H, 19-H, 20-H), 7.83 (br. s, 1 H, NH), 8.06 (d, $^3J_{NH,15}$ = 7.8 Hz, 1 H, NH), 8.82 (br. s, 1 H, OH), 10.46 (br. s, 1 H, NH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 25.4 (q, C-22), 27.7 (t, C-7), 28.1 (qt, C-5, C-8), 35.1 (t, C-9), 37.1 (t, C-16), 47.7 (d, C-6), 53.3 (d, C-2), 54.2 (d, C-15), 78.1 (s, C-4), 125.5 (d, C-13), 126.1 (d, C-20), 128.0, 128.1, 128.9 (4 d, C-11, C-12, C-18, C-19), 137.9 (s, C-17), 142.0 (s, C-10), 155.0 (s, C-3), 167.4 (s, C-1), 171.1 (s, C-14), 171.6 (s, C-21) ppm. HRMS (CI): calcd. for $C_{28}H_{39}N_4O_5$ [M – O + H]$^+$ 511.2876; found 511.2871.

***N*-Methyl-(*R*)-2-[(*R*)-2-(hydroxyamino)-1-(2-hydroxyacetylamino)-2-oxoethyl]-5-phenylpentanoyl-(*S*)-phenylalanineamide (1b):** A solution of **11b** (51 mg, 89 μmol) in dry DMF (3 mL) was hydrogenated with Pd/C (10%, 10 mg) until completion of the reaction. The Pd/C was filtered off and the filtrate was concentrated in vacuo. The crude product was triturated with methanol to yield hydroxamic acid **1b** (36 mg, 74 μmol, 84%) as a white solid; m.p. 175–180 °C (dec.); $[\alpha]_D^{20}$ = –5.8 (*c* = 0.6, DMF). ^{1}H NMR ([D$_6$]DMSO): δ = 1.24–1.53 (m, 4 H, 6-H, 7-H), 2.39 (m, 2 H, 8-H), 2.51 (m, 3 H, 21-H), 2.63 (m, 1 H, 5-H), 2.87 (dd, $^2J_{15a,15b}$ = 13.2, $^3J_{15a,14}$ = 7.3 Hz, 1 H, 15-H$_a$), 3.00 (dd, $^2J_{15b,15a}$ = 13.4, $^3J_{15b,14}$ = 5.8 Hz, 1 H, 15-H$_b$), 3.82 (d, $^3J_{4,OH}$ = 5.2 Hz, 1 H, 4-H), 4.40 (m, 1 H, 14-H), 4.40 (dd, $^3J_{2,5}$ = $^3J_{2,NH}$ = 8.3 Hz, 1 H, 2-H), 5.50 (t, $^3J_{OH,4}$ = 5.3 Hz, 1 H, OH), 7.09–7.26 (m, 10 H, 10-H, 11-H, 12-H, 17-H, 18-H, 19-H), 7.61 (d, $^3J_{NH,2}$ = 8.9 Hz), 7.84 (br. s, 1 H, NH), 6.08 (d, $^3J_{NH,14}$ = 7.7 Hz, 1 H, NH), 8.91 (br. s, 1 H, OH), 10.60 (br. s, 1 H, NH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 25.5 (q, C-21), 27.5 (t, C-6), 28.3 (t, C-7), 35.1 (t, C-8), 37.2 (t, C-15), 47.8 (d, C-5), 51.3 (d, C-2), 54.2 (d, C-14), 61.2 (t, C-4), 125.5 (d, C-12), 126.1 (d, C-19), 128.0, 128.1, 128.9 (4 d, C-10, C-11, C-17, C-18), 138.0 (s, C-16), 142.0 (s, C-9), 166.7 (s, C-1), 171.0, 171.1, 171.3 (3 s, C-3, C-13, C-20) ppm. HRMS (CI): calcd. for $C_{25}H_{32}N_4O_6$ [M + H]$^+$ 485.2400; found 485.2432.

***N*-Methyl-(*R*)-2-[(*R*)-2-(hydroxyamino)-1-(acetylamino)-2-oxoethyl]-5-phenylpentanoyl-(*S*)-phenylalanineamide (1c):** A solution of **11c** (35 mg, 63 μmol) in dry DMF (14 mL) was hydrogenated with Pd/C (10%, 8 mg). After completion of the reaction the Pd/C was filtered off and the filtrate was concentrated in vacuo. The crude product was triturated with methanol to yield hydroxamic acid **1c** (26 mg, 55 μmol, 88%) as a white solid; m.p. 208–210 °C (dec.); $[\alpha]_D^{20}$ = +12.8 (*c* = 0.6, DMSO). ^{1}H NMR ([D$_6$]DMSO): δ = 1.28 (m, 2 H, 7-H), 1.40 (m, 2 H, 6-H), 1.82 (s, 3 H, 4-H), 2.37 (m, 1 H, 8-H$_a$), 2.44 (m, 1 H, 8-H$_b$), 2.51 (d, $^3J_{21,NH}$ = 5.0 Hz, 3 H, 21-H), 2.60 (m, 1 H, 5-H), 2.85 (dd, $^2J_{15a,15b}$ = 13.7, $^3J_{15a,14}$ = 7.9 Hz, 1 H, 15-H$_a$), 2.98 (dd, $^2J_{15b,15a}$ = 13.7, $^3J_{15b,14}$ = 6.2 Hz, 1 H, 15-

H_b), 4.37 (m, 1 H, 14-H), 4.49 (dd, $^3J_{2,5}$ = $^3J_{2,NH}$ = 9.1 Hz, 1 H, 2-H), 7.08–7.25 (m, 10-H, 11-H, 12-H, 17-H, 18-H, 19-H), 7.82 (q, $^3J_{NH,21}$ = 4.5 Hz, 1 H, NH), 8.00 (d, $^3J_{NH,2}$ = 9.2 Hz, 1 H, NH), 8.12 (d, $^3J_{NH,14}$ = 7.7 Hz, 1 H, NH), 8.82 (s, 1 H, OH), 10.51 (s, 1 H, NH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 22.4 (q, C-4), 25.4 (q, C-21), 27.8 (t, C-7), 28.1 (t, C-6), 35.0 (t, C-8), 37.1 (t, C-15), 47.6 (d, C-5), 51.3 (d, C-2), 54.2 (d, C-14), 125.4 (d, C-12), 126.0 (d, C-19), 128.0, 128.1, 128.9 (4 d, C-10, C-11, C-17, C-18), 137.9 (s, C-16), 142.0 (s, C-9), 167.1 (s, C-1), 169.1 (s, C-3), 171.1 (s, C-20), 171.6 (s, C-13) ppm. HRMS (CI): calcd. for $C_{25}H_{30}N_3O_4$ [M – NHOH]$^+$ 436.2237; found 436.2235.

***N*-Methyl-(*R*)-2-[(*R*)-2-(hydroxyamino)-1-(benzoylamino)-2-oxoethyl]-5-phenylpentanoyl-(*S*)-phenylalanineamide (1d):** A solution of **11d** (39 mg, 63 μmol) in dry DMF (14 mL) was hydrogenated with Pd/C (10%, 8 mg), the Pd/C was filtered off and the filtrate was concentrated in vacuo. The crude product was triturated with methanol to yield hydroxamic acid **1d** (25 mg, 47 μmol, 75%) as a white solid; m.p. 225–228 °C (dec.); $[\alpha]_D^{20}$ = +7.9 (*c* = 0.9, DMSO). ^{1}H NMR ([D$_6$]DMSO): δ = 1.29 (m, 2 H, 7-H), 1.48 (m, 2 H, 6-H), 2.40 (m, 2 H, 8-H), 2.53 (d, $^3J_{21,NH}$ = 3.7 Hz, 3 H, 21-H), 2.78 (m, 1 H, 5-H), 2.89 (m, 1 H, 15-H_a), 2.98 (dd, $^2J_{15b,15a}$ = 13.6, $^3J_{15b,14}$ = 5.3 Hz, 1 H, 15-H_b), 4.40 (m, 1 H, 14-H), 4.73 (dd, $^3J_{2,5}$ = $^3J_{2,NH}$ = 8.7 Hz, 1 H, 2-H), 7.05–7.20 (m, 10-H, 11-H, 12-H, 17-H, 18-H, 19-H), 7.46 (m, 2 H, 23-H), 7.54 (m, 1 H, 24-H), 7.82 (d, $^3J_{22,23}$ = 7.2 Hz, 1 H, 22-H), 7.91 (q, $^3J_{NH,21}$ = 3.1 Hz, 1 H, NH), 8.21 (d, $^3J_{NH,14}$ = 7.7 Hz, 1 H, NH), 8.41 (d, $^3J_{NH,2}$ = 8.4 Hz, 1 H, NH), 8.87 (s, 1 H, OH), 10.57 (s, 1 H, NH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 25.5 (q, C-21), 27.9 (t, C-7), 28.1 (t, C-6), 35.0 (t, C-8), 37.0 (t, C-15), 47.3 (d, C-5), 52.3 (d, C-2), 54.3 (d, C-14), 125.4 (d, C-12), 126.1 (d, C-19), 127.5 (d, C-22), 128.0, 128.1, 128.9 (5 d, C-10, C-11, C-17, C-18, C-23), 131.3 (d, C-24), 131.3 (s, C-4), 138.1 (s, C-16), 141.9 (s, C-9), 166.3 (s, C-1), 167.2 (s, C-3), 171.2, 171.8 (2 s, C-13, C-20) ppm. HRMS (CI): calcd. for $C_{30}H_{32}N_3O_4$ [M – NHOH]$^+$ 498.2393; found 498.2366.

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