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Synthesis of Simplified Halogenated Chondramide Derivatives with Strong Cytostatic Properties

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Removing the methyl groups and the stereogenic centers from the ω-hydroxy acid of the chondramides results in a significant drop in the cytotoxicity of these interesting depsipeptides. This effect can be almost compensated for by introduction of a second chlorine atom on the β-tyrosine moiety of the natural products. These simplified chondramides are much easier accessible than natural chondramides.

Introduction

Cyclic peptides and depsipeptides are very suitable candidates for the development of drugs, because many of them show interesting biological activities.[1] In most cases these cyclic peptides are produced by microorganisms. The first members of a rather large group of cyclodepsipeptides (Figure 1), jasplakinolide[2] and geodiamolides[3] have been isolated from sponges and were described as cytotoxic compounds in the late 80's. Because of this interesting biological activity, shortly thereafter the first syntheses for geodiamolides[4] and jasplakinolide were described.[5] For jasplakinolide, in particular, a wide range of syntheses have been developed, which were nicely covered in a recent review.[6]

In 1995 Höfle and Reichenbach reported the isolation of a closely related class of compounds named chondramides,[7] which mainly differ in the polyketide fragment. For chondramides, as well as analogues, several syntheses have been reported.[8]

With enough synthetic material in hand, detailed biological studies could be carried out. Geodiamolide was found to regulate the actin cytoskeleton, migration and invasion of breast cancer cells.[9] The most detailed studies have been carried out with jasplakinolide and its analogues. Most effects can be explained by a stabilization of the actin skeleton,[10] by altering, for example, anaphase chromosome movements.[11] Apoptosis is induced in a wide range of cancer cell lines.[12] The chondramides were shown to bind to actin in an analogous manner, what makes these substances of significant interest to our research group.[8b]

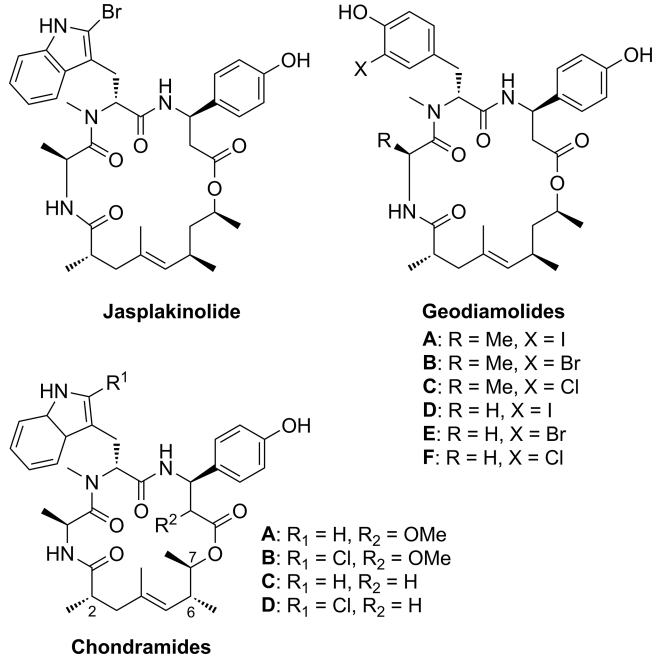

Figure 1. Actin-stabilizing cyclodepsipeptides.

The structures of these cyclopeptides (Figure 1) are closely related. The highly conserved tripeptide moiety contains an *N*-terminal (*S*)-alanine, a *N*-methylated (*R*)-aromatic amino acid (tryptophan or tyrosine), and a *C*-terminal (*R*)-β-tyrosine. Interestingly, the central *N*-methylated aromatic amino acids are generally halogenated, even in some products obtained from terrestrial myxobacteria (chondramides).

Halogenation seems to be essential for strong actin binding, because halogenated chondramides show higher cytotoxicity towards a wide range of tumor cell lines (low nM range) relative to non-halogenated ones.[13] Very recently,

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Müller et al. isolated several more chondramides that also contain halogenated β-tyrosines.[14]

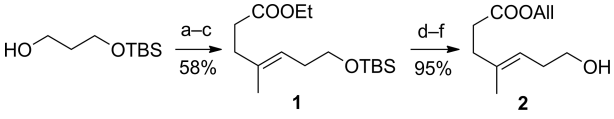
The unsaturated polyketide fragment of the chondramides slightly differs in the chain length and substitution pattern from the other depsipeptides, especially at the end of the chain. One might assume that this part of the molecule might not be involved in binding and/or biological activity. Therefore, structural modifications and simplifications might be possible in this area.

During their syntheses of the chondramides, Kalesse[8a] as well as Waldmann and Arndt et al.[8b] investigated the influence of the three methyl groups on biological activity by using a library of all possible stereoisomers. No big change in activity was observed when the two methyl groups at C-6 and C-7 were inverted. In contrast, a significant drop was observed if only one group was changed. The *N*-terminal alanine can be replaced by a protected lysine, what also allows the incorporation of fluorescence labels at this position.[15] Maier et al. could show that in the *C*-terminal β-tyrosine the OH group can be replaced by several other substituents without dramatically changing the activity.[8d]

Because our group is involved in the synthesis of antitumor-active natural products and simplified analogues thereof, we were interested to see, if it is not possible to remove the methyl groups completely.[16] We hoped that by simultaneous change of the halogenation pattern in the peptide fragment the biological activity might (at least in part) remain.

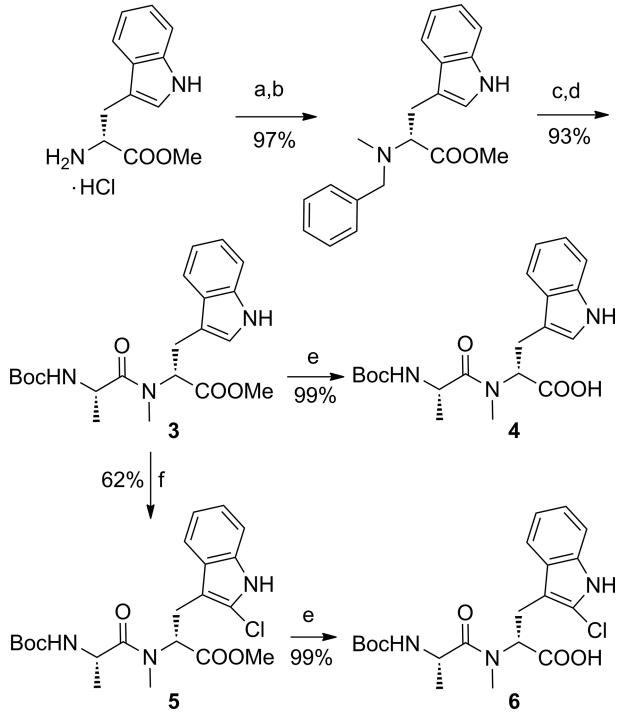
Results and Discussion

The protected unsubstituted ω-hydroxy acid was easily obtained from *tert*-butyldimethylsilyl (TBS)-protected propanediol (Scheme 1). Swern oxidation and subsequent isopropenyl-Grignard addition provided the corresponding allyl alcohol, which was subjected to Johnson–Claisen-rearrangement to give rise to *O*-silylated ethyl ester **1**.[17] Originally, we tried to couple this ester directly with the tripeptide fragment, but later on we were not able to cleave the ethyl ester selectively in the presence of the tripeptide ester. Therefore, ester **1** was saponified and the free acid was converted into the corresponding allyl ester. Finally, the silyl protecting group was removed under standard conditions to give required building block **2** in excellent yield.



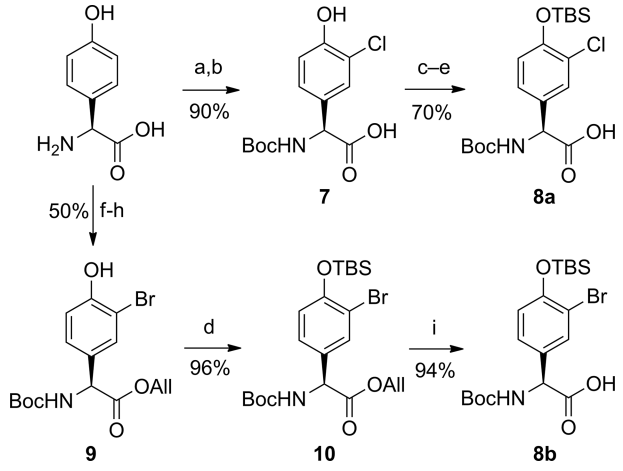
Scheme 1. Synthesis of ω-hydroxy acid **2**. (a) DMSO, $(COCl)_2$, Et_3N, abs. CH_2Cl_2, –78 °C to room temp.; (b) isopropenyl-MgBr, abs. THF, 0 °C to room temp.; (c) propionic acid, $H_3CC(OEt)_3$, reflux, 16 h; (d) NaOH, EtOH; (e) allyl bromide, K_2CO_3, DMF, 0 °C to room temp.; (f) TBAF·$3H_2O$, abs. THF, room temp., 16 h.

For the synthesis of the tripeptide fragment we started with tryptophan methyl ester, which was converted into the *N*-methylated *N*-benzylated derivative[18] in a straightforward one-pot protocol (Scheme 2). The benzyl protecting group was removed through hydrogenation and the secondary amine was coupled with *N*-*tert*-butoxycarbonyl (Boc) protected alanine. Although T3P® (propylphosphonic anhydride) in combination with Hünig's base gave coupling product **3** in only 47%, an excellent yield was obtained by using *N*,*N*′-dicyclohexylcarbodiimide (DCC) and hydroxybenzotriazole (HOBT).[8a] Saponification of **3** with NaOH gave access to free acid **4** in enantiomerically pure form. To obtain the chlorinated dipeptide, **3** was treated with *N*-chlorosuccinimide (NCS) in the presence of dibenzoyl peroxide at –20 °C to dipeptide **5**,[19] which was saponified in quantitative yield to give acid **6**.



Scheme 2. Synthesis of dipeptide fragments **4** and **6**. (a) Benzaldehyde, MeOH, $NaCNBH_3$, AcOH, 16 h, room temp.; (b) $(CH_2O)_n$, 4 h, $NaCNBH_3$, AcOH, 48 h, r.t.; (c) H_2 (40 psi), Pd/C, MeOH, 1 h, r.t.; (d) *N*-Boc-(*S*)-AlaOH, DCC, HOBt, THF, 0 °C to r.t., 16 h; (e) NaOH, THF, 4 h, r.t.; (f) NCS, dibenzoyl peroxide, CH_2Cl_2, –20 °C to r.t., 16 h.

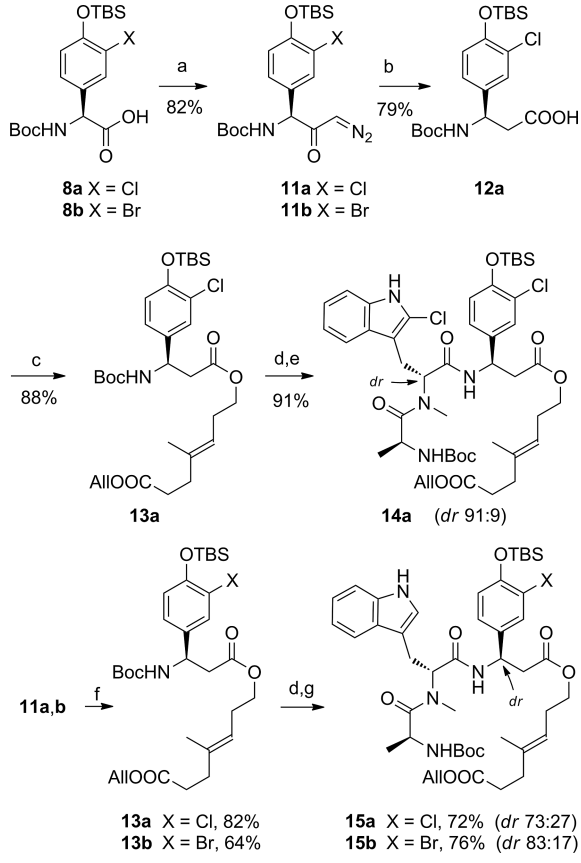
For the synthesis of halogenated β-tyrosine derivatives we used the Arndt–Eistert protocol, which was also applied in the jasplakinolide synthesis.[20] Commercially available 4-hydroxyphenylglycine was chlorinated by using SO_2Cl_2 in acetic acid (Scheme 3).[21] To avoid side reactions during further synthesis, the amino group was Boc-protected. With NaOH as a base partial epimerization of the stereogenic center was observed and the *ee* value varied as a function of reaction time. This problem could be solved by using $NaHCO_3$ as a base, which provided **7** in excellent yield and enantiomerically pure. The free carboxylic acid was subsequently converted into the corresponding benzyl ester, which was silylated at the phenolic group. During the benzylation partial benzyl ether formation was observed, but this side product was removed easily by chromatography.



Scheme 3. Synthesis of halogenated β-tyrosines **8a** and **8b**. (a) SO_2Cl_2, AcOH, room temp., 16 h; (b) Boc_2O, $NaHCO_3$, THF/H_2O, 0 °C to r.t., 16 h; (c) BnBr, $NaHCO_3$, DMF, r.t., 16 h; (d) TBSCl, imidazole, DMF, 0 °C to r.t., 16 h; (e) H_2, Pd/C, MeOH, r.t., 1 h; (f) HBr/AcOH, Br_2, AcOH, r.t., 24 h; (g) Boc_2O, NaOH, dioxane/H_2O, 0 °C to r.t., 16 h; (h) allyl bromide, K_2CO_3, DMF, r.t., 16 h; (i) $Pd(PPh_3)_4$, morpholine, THF, room temp., 2 h.

After silylation the benzyl ester was cleaved by hydrogenation to free acid **8a**[22] and the benzyl ether side product could be reconverted into **7**. For the synthesis of brominated analogue **8b** the synthetic protocol had to be changed slightly because hydrogenolytic cleavage of the benzyl ester is not compatible with the aryl bromide. The bromine was introduced by using HBr and Br_2,[23] and during Boc-protection partial epimerization was observed (62% *ee*). The formation of allyl ester **9** was accompanied by undesired phenol allylation but the side product was removed easily. Silylation of the phenolic OH group (**10**) and subsequent cleavage of the allyl ester with $Pd(PPh_3)_4$/morpholine[24] provided brominated amino acid **8b** in high yield and without further epimerization of the stereogenic center.

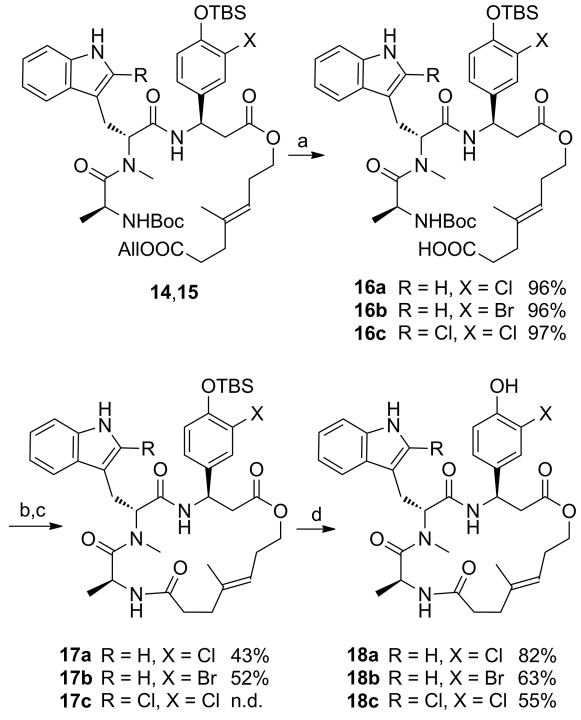
Two protected amino acids **8** were converted into corresponding diazo ketones **11** (Scheme 4). Interestingly, only ethyl chloroformate as an activating reagent gave acceptable yields, whereas other chloroformates failed. To avoid epimerization of the activated amino acid, the diazomethane solution had to be free of traces of base. This solution was freshly prepared from nitrosourea and 40% KOH solution. Before use, the ethereal CH_2N_2 solution was washed with H_2O and brine. Under these conditions two diazo ketones **11** were obtained in 82% yield without (further) epimerization. Chloro derivative **11a** was used to optimize the conditions for the Arndt–Eistert reaction. Under standard reaction conditions by using several Ag-salts in tetrahydrofuran (THF)/H_2O yields in the range of 55–65% could be obtained. The best results gave a very recent procedure, in which diazo ketone was dissolved in ethyl acetate and silver benzoate and silica were added in the dark.[25] After 3 h desired β-amino acid **12a** could be obtained in enantiomerically pure form, which could directly be coupled to ω-hydroxy acid **2**. To figure out if esterification can directly be combined with the Arndt–Eistert homologization, we subjected partially epimerized halogenated amino acids **11a** and **11b** to the Wolff rearrangement and trapped the ketene intermediate formed directly with ω-hydroxy ester **2**. This ester was used in twofold excess, and the excess was easily recovered by flash chromatography. Chloro derivative **13a** was obtained in high yield and without further epimerization, the yield for bromo analogue **13b** was slightly worse. The *N*-Boc-protecting group was removed at –20 °C and the free amines were directly coupled with dipeptides **4** and **6**. The deprotection reaction had to be carried out at this low temperature to avoid simultaneous deprotection of the phenolic silyl protecting group. Interestingly, during the activation of chlorinated dipeptide **6** a slight epimerization of chlorotryptophane occurred (*dr* 91:9), whereas no epimerization was observed during coupling of non-halogenated peptide **4**.



Scheme 4. Synthesis of cyclization precursors **14** and **15**. (a) (1) ClCOOEt, Et_3N, THF, –20 °C, 20 min; (2) –78 °C, CH_2N_2, –78 °C to room temp. (**11a**), 16 h, or –78 °C to –15 °C (**11b**), 16 h; (b) AgOBz, SiO_2, EtOAc, 45 °C, 3 h, dark; (c) **2**, DCC, DMAP, Et_2O, –20 °C to r.t., 16 h; (d) (1) CF_3COOH, CH_2Cl_2, –20 °C, 16 h; (2) $NaHCO_3$; (e) **6**, COMU® [(1-cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate], iPr_2NEt, 0 °C to r.t., 16 h; (f) **11a/b**, AgOBz, Et_3N, THF, –25 °C, 16 h, dark; (g) **4**, COMU®, iPr_2NEt, 0 °C to r.t., 16 h.

Because enantiomerically pure **13a** was coupled with **6**, the two diastereomers formed differ in the configuration of the *N*-methyltryptophan, whereas diastereomers of **15a** and **15b** are partially epimerized at the β-tyrosine. But the formation of the diastereomeric products was not of great im-

portance because the isomers could be separated later on on the cyclic depsipeptide. To get access to these, allyl esters of **14** and **15** were removed under Pd-catalysis.[24] Our initial route with the ethyl ester (obtained through Claisen rearrangement) failed at this point, because we could not find a protocol that cleaved the ethyl ester selectively in the presence of the tripeptide ester. However, allyl ester cleavage did not cause any problem. Subsequently, the *N*-Boc-protecting group was removed at –20 °C and the deprotected peptide ester was cyclized by using T3P[26] and diisopropylethylamine under high dilution conditions. On this stage the stereoisomers could easily be separated and desired peptides **17** were obtained in enantiomerically pure form in acceptable yield. Finally the phenolic silyl group was removed with tetrabutylammonium fluoride (TBAF) to give rise to desired simplified chondramide derivatives **18** (Scheme 5).



Scheme 5. Synthesis of simplified chondramide derivatives **18**. (a) $Pd(PPh)_4$, morpholine, THF; (b) CF_3COOH, CH_2Cl_2, –20 °C, 16 h; (c) T3P®, iPr_2NEt, CH_2Cl_2, 0 °C to room temp., 16 h; (d) Bu_4NF, THF, r.t.

The biological activity of these three derivatives were investigated[14] towards different cancer cell lines and the results were analyzed relative to fully methylated but non halogenated chondramide C. Chondramide C shows activity towards several cell lines in the GI_{50}-range of 30 nM. Complete removal of the methyl groups and monohalogenation at the β-tyrosine unit results in a dramatic drop in activity and shifts the GI_{50} values into the low μM range. To our surprise double chlorinated derivative **18c** showed the same activity towards HCT-116 cells as chondramide C. The data were slightly worse in the case of U-2OS cells and dropped by a factor 10 for KB-3.1 cells. Obviously, the new derivative is more sensitive towards the different cell lines, but the example clearly illustrates that the structure and synthesis can be simplified significantly if the aromatic amino acids are both chlorinated (Table 1).

Table 1. Cytotoxicity of chondramide derivatives **18** towards tumor cells.[14]

	GI_{50}[a] [nM] HCT-116[b]	KB-3.1[c]	U-2OS[d]
Chondramide C	34	37	26
18a	1300	4800	2800
18b	2100	6400	1800
18c	30	376	67

[a] 50% of maximal inhibition of cell proliferation. [b] Human colon cancer. [c] Human cervical carcinoma. [d] Human bone osteosarcoma.

Conclusions

In conclusion, we have shown that the structure of chondramides can be significantly simplified by removing all methyl groups, and with them all stereogenic centers, from the hydroxy carboxylic acid. As long as both aromatic amino acids are chlorinated comparable antitumor-activities as for chondramide C, at least towards some cancer cell lines, are observed. Further modifications on the chondramide skeleton are currently under investigation.

Experimental Section

General Remarks: All air- or moisture-sensitive reactions were carried out in dried glassware (> 100 °C) under an atmosphere of nitrogen or argon. Dried solvents were distilled before use: THF was distilled from $LiAlH_4$, dichloromethane and dimethylformamide (DMF) were purchased from Sigma–Aldrich. Diazomethane was prepared in special glassware. The products were purified by flash chromatography on silica gel (0.063–0.2 mm). Mixtures of EtOAc and petroleum ether were generally used as eluents. Analytical TLC was performed on pre-coated silica gel plates (Macherey–Nagel, Polygram® SIL G/UV254). Visualization was accomplished with UV-light, $KMnO_4$ solution or ninhydrin solution. Melting points were determined with a Dr. Tottoli (Büchi) melting point apparatus. ^1H and ^{13}C NMR spectra were recorded with a Bruker AC-400 [400 MHz (^1H) and 100 MHz (^{13}C)]. Chemical shifts are reported in ppm relative to residual solvent. Diastereomeric ratios were determined by NMR spectroscopy or HPLC. Selected signals of minor isomers were extracted from the NMR spectra of the isomeric mixtures. The enantiomeric and diastereomeric ratios were determined by HPLC by using a chiral column (Reprosil 100 Chiral-NR 8 μm). Mass spectra were recorded with a Finnigan MAT 95 spectrometer (quadrupole) by using the CI technique. HPLC/MS analysis was performed with a Shimadzu system (LC: 10A-series + Autosampler, MS: LCMS-2020) and an achiral column (Luna 3μ C18, 50 × 4.6 mm). Elemental analyses were performed at the Saarland University.

Ethyl (*E*)-7-(*tert*-Butyldimethylsiloxy)-4-methylhept-4-enoate (1):[17] To a solution of oxalyl chloride (1.58 mL, 18.4 mmol) in abs. CH_2Cl_2 (47 mL) a solution of abs. DMSO (2.61 mL, 36.7 mmol) in abs. CH_2Cl_2 (15 mL) was added at –78 °C. After 30 min 3-(*tert*-butyldimethylsilyloxy)propan-1-ol (2.85 g, 15.0 mmol) in abs. CH_2Cl_2 (40 mL) was added and the solution was stirred for 60 min,

before Et_3N (6.26 mL, 44.9 mmol) was added dropwise. The mixture was warmed to room temperature over 2 h, diluted with water and the organic layer was extracted with CH_2Cl_2. The combined extracts were washed with HCl (1 M), H_2O, satd. $NaHCO_3$ and brine, dried with Na_2SO_4 and concentrated under reduced pressure (> 400 mbar) to provide 3-(*tert*-butyldimethylsilyloxy)propanal as a pale yellow oil.

The crude aldehyde was slowly added to isopropenylmagnesium bromide solution (44.2 mL, 22.1 mmol, 0.5 M in THF) at 0 °C. The mixture was warmed to room temperature overnight, hydrolyzed with satd. NH_4Cl and extracted with diethyl ether. The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated in vacuo to obtain 5-(*tert*-butyldimethylsilyloxy)-2-methylpent-1-en-3-ol as a pale yellow oil.

The crude allyl alcohol and propionic acid (59.0 μL, 0.79 mmol) were dissolved in triethyl orthoacetate (17.0 mL, 94.6 mmol) and the mixture was heated to reflux overnight. After complete consumption of the alcohol the solvent was removed under reduced pressure (40 mbar, 140 °C) with a Vigreux column. Purification by flash chromatography (petroleum ether/ethyl acetate, 95:5) provided **1** (2.65 g, 8.65 mmol, 58%) as a colorless oil. R_f = 0.38 (petroleum ether/ethyl acetate, 95:5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 6 H), 0.89 (s, 9 H), 1.24 (t, J = 7.2 Hz, 3 H), 1.62 (s, 3 H), 2.21 (dt, J = 7.2, 7.2 Hz, 2 H), 2.30 (m, 2 H), 2.39 (m, 2 H), 3.56 (t, J = 7.2 Hz, 2 H), 4.11 (q, J = 7.3 Hz, 2 H), 5.15 (tq, J = 7.2, 1.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3, 14.2, 16.1, 18.3, 25.9, 31.8, 33.2, 34.7, 60.2, 62.9, 121.2, 135.3, 173.4 ppm.

Allyl (*E*)-7-Hydroxy-4-methylhept-4-enoate (2): To a solution of unsaturated ethyl ester **1** (2.12 g, 7.06 mmol) in EtOH (25 mL) NaOH (1 M, 7.77 mL, 7.77 mmol) was added dropwise at 0 °C. After warming to room temperature overnight, the solvent was removed under reduced pressure and the residue was taken up in H_2O. The aqueous solution was acidified to pH 2–3 with $KHSO_4$ (1 M) and extracted with ethyl acetate. The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated in vacuo to provide crude (*E*)-7-(*tert*-butyldimethylsiloxy)-4-methyl-hept-4-enoic acid as a colorless oil.

To a solution of the crude acid in abs. DMF (25 mL) K_2CO_3 (1.95 g, 14.1 mmol) and allyl bromide (1.28 g, 20.6 mmol) were added at 0 °C. After being warmed to room temperature overnight, the mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layers were further washed with H_2O and brine, dried with Na_2SO_4 and evaporated under reduced pressure to obtain crude (*E*)-7-(*tert*-butyldimethylsiloxy)-4-methyl-hept-4-enoic acid allyl ester.

The crude allyl ester was dissolved in abs. THF (25 mL), treated with TBAF·3H_2O (2.03 g, 7.77 mmol) and stirred overnight at room temperature. The mixture was diluted with ethyl acetate and washed with HCl (1 M) and brine and dried with Na_2SO_4. Removal of the solvent under reduced pressure and purification by flash chromatography (petroleum ether/ethyl acetate, 8:2) resulted in the isolation of **2** (1.33 g, 6.71 mmol, 95%) as a colorless oil. R_f = 0.14 (petroleum ether/ethyl acetate, 8:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.58 (br. s, 1 H, OH), 1.66 (s, 3 H), 2.27 (dt, J = 6.5, 6.5 Hz, 2 H), 2.35 (m, 2 H), 2.46 (m, 2 H), 3.60 (t, J = 6.3 Hz, 2 H), 4.56 (ddd, J = 5.8, 1.3, 1.3 Hz, 2 H), 5.16 (tq, J = 7.3, 1.3 Hz, 1 H), 5.23 (ddt, J = 10.3, 1.3, 1.3 Hz, 1 H), 5.31 (ddt, J = 17.3, 1.5, 1.5 Hz, 1 H), 5.90 (ddt, J = 17.1, 10.3, 5.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.1, 31.4, 32.9, 34.8, 62.2, 65.1, 118.2, 121.1, 132.2, 136.8, 173.0 ppm. HRMS (CI): *m*/*z* calcd. $C_{11}H_{19}O_3$ $[M + H]^+$ 199.1329; found 199.1346.

***N*-*tert*-Butoxycarbonyl-(*S*)-alanyl-*N*-methyl-(*R*)-tryptophan Methyl Ester (3):**[8a] (*R*)-Tryptophan methyl ester hydrochloride (5.00 g, 19.6 mmol) was dissolved in satd. $NaHCO_3$ and the resulting solution was extracted with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4 and the solvent was removed under reduced pressure. To a solution of the crude product in abs. MeOH (150 mL), $NaCNBH_3$ (1.42 g, 22.6 mmol), benzaldehyde (2.29 g, 21.6 mmol) and acetic acid (1.18 g, 19.6 mmol) were added at room temperature. After 16 h at this temperature paraformaldehyde (1.95 g, 21.6 mmol), $NaCNBH_3$ (1.42 g, 22.6 mmol) and acetic acid (1.18 g, 19.6 mmol) were added. After a further 16 h, the solvent was removed under reduced pressure, the residue was dissolved in satd. $NaHCO_3$, the aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried with Na_2SO_4. Removal of the solvent under reduced pressure and purification by flash chromatography (hexanes/ethyl acetate, 7:3) resulted in the isolation of *N*-benzyl-*N*-methyl-(*R*)-tryptophan methyl ester[18a] (6.15 g, 19.1 mmol, 97%) as a colorless solid, m.p. 81–83 °C. R_f = 0.27 (hexanes/ethyl acetate, 7:3). $[\alpha]_D^{20}$ = +59.7 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.40 (s, 3 H), 3.14 (dd, J = 14.4, 5.9 Hz, 1 H), 3.38 (dd, J = 14.3, 9.0 Hz, 1 H), 3.65–3.68 (m, 4 H), 3.78 (dd, J = 8.9, 5.9 Hz, 1 H), 3.89 (d, J = 13.6 Hz, 1 H), 7.02 (d, J = 2.0 Hz, 1 H), 7.11 (dd, J = 7.4, 7.4 Hz, 1 H), 7.20 (dd, J = 7.4, 7.4 Hz, 1 H), 7.25–7.40 (m, 6 H), 7.52 (d, J = 8.0 Hz, 1 H), 8.01 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.6, 38.2, 50.9, 58.8, 66.3, 111.0, 112.2, 118.6, 119.2, 121.8, 122.6, 126.9, 127.5, 128.2, 128.8, 136.1, 139.3, 172.6 ppm. HRMS (CI): *m*/*z* calcd. for $C_{20}H_{23}N_2O_2$ $[M + H]^+$ 323.1754; found 323.1719.

A mixture of *N*-benzyl-*N*-methyl-(*R*)-tryptophan methyl ester (5.64 g, 17.5 mmol) and Pd/C (10%, 1.86 g) in abs. MeOH (135 mL) was stirred under a hydrogen atmosphere (40 psi, room temp.) for 1 h. Filtration over Celite and removal of the solvent under reduced pressure resulted in the isolation of *N*-methyl-(*R*)-tryptophan methyl ester (4.04 g, 17.4 mmol, 99%) as a pale yellow oil. R_f = 0.08 (petroleum ether/ethyl acetate, 1:1). $[\alpha]_D^{20}$ = –45.7 (c = 1.0, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, 3 H), 3.12 (dd, J = 14.6, 7.3 Hz, 1 H), 3.20 (dd, J = 14.3, 6.0 Hz, 1 H), 3.57 (dd, J = 7.2, 6.2 Hz, 1 H), 3.67 (s, 3 H), 7.02 (d, J = 2.5 Hz, 1 H), 7.12 (ddd, J = 7.8, 7.8, 1.0 Hz, 1 H), 7.19 (ddd, J = 7.3, 7.3, 1.3 Hz, 1 H), 7.34 (d, J = 8.0 Hz, 1 H), 7.62 (d, J = 7.8 Hz, 1 H), 8.26 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.1, 34.8, 51.7, 63.8, 111.1, 111.2, 118.7, 119.4, 122.0, 122.8, 127.4, 136.2, 175.1 ppm.

To a solution of *N*-methyl-*(R)*-tryptophan methyl ester (4.01 g, 17.3 mmol) and *N*-Boc-L-alanine (3.60 g, 19.0 mmol) in abs. diethyl ether (130 mL) HOBt·H_2O (265 mg, 1.73 mmol) and DCC (3.92 g, 19.0 mmol) were added at 0 °C before the mixture was warmed to room temperature overnight. The precipitate was filtered and the organic layer was washed twice with $KHSO_4$ (1 M), H_2O, satd. $NaHCO_3$ and brine, dried with Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (hexanes/ethyl acetate, 1:1) provided dipeptide **3** (6.56 g, 16.3 mmol, 94%) as a colorless solid, m.p. 68–69 °C. R_f = 0.25 (hexanes/ethyl acetate, 1:1). $[\alpha]_D^{20}$ = +54.3 (c = 1.0, $CHCl_3$). 89:11 Mixture of rotamers. Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (d, J = 6.8 Hz, 3 H), 1.43 (s, 9 H), 2.82 (s, 3 H), 3.29 (dd, J = 15.3, 11.0 Hz, 1 H), 3.46 (dd, J = 15.6, 4.3 Hz, 1 H), 3.75 (s, 3 H), 4.49 (dq, J = 7.3, 7.3 Hz, 1 H), 5.28 (dd, J = 11.0, 5.0 Hz, 1 H), 5.46 (d, J = 7.8 Hz, 1 H), 6.99 (d, J = 2.3 Hz, 1 H), 7.11 (ddd, J = 7.3, 7.3, 1.0 Hz, 1 H), 7.18 (ddd, J = 7.0, 7.0, 1.3 Hz, 1 H), 7.34 (d, J = 7.8 Hz, 1 H), 7.58 (d, J = 7.8 Hz, 1 H), 8.25 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.3, 24.4, 28.3, 32.8, 46.5, 52.3, 58.1, 79.5, 110.7, 111.2, 118.3, 119.5, 122.1, 122.4, 127.1, 136.1, 155.1, 171.1, 173.4 ppm. Minor

rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 9 H), 2.92 (s, 3 H), 3.20 (dd, J = 15.0, 8.8 Hz, 1 H), 3.46 (dd, J = 15.0, 6.3 Hz, 1 H), 4.42 (m, 1 H), 4.84 (dd, J = 8.0, 6.5 Hz, 1 H), 5.10 (br. s, 1 H), 7.04 (br. s, 1 H), 7.63 (d, J = 7.3 Hz, 1 H), 8.21 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.9, 46.1, 52.6, 60.2, 119.8 ppm.

***N-tert*-Butoxycarbonyl-(*S*)-alanyl-*N*-methyl-(*R*)-tryptophan (4):**[8a] To a solution of dipeptide **3** (4.84 g, 12.0 mmol) in THF (72 mL) NaOH (0.4 M, 36.0 mL, 14.4 mmol) was added at 0 °C. After warming to room temperature overnight, the solvent was removed under reduced pressure and the residue was dissolved in H_2O. The aqueous solution was acidified to pH 3 with HCl (2 M) and extracted with ethyl acetate. The combined organic layers were dried with Na_2SO_4 and the solvents evaporated in vacuo to yield **4** (4.67 g, 12.0 mmol, 99%) as a colorless foam. R_f = 0.17 [petroleum ether/ethyl acetate (1:1) + 1% AcOH]. $[\alpha]_D^{20}$ = +37.1 (c = 1.0, $CHCl_3$). 89:11 Mixture of rotamers. Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (d, J = 6.8 Hz, 3 H), 1.43 (s, 9 H), 2.82 (s, 3 H), 3.34 (dd, J = 15.3, 11.0 Hz, 1 H), 3.49 (dd, J = 15.6, 4.5 Hz, 1 H), 4.51 (dq, J = 7.5, 7.5 Hz, 1 H), 5.30 (dd, J = 10.9, 4.6 Hz, 1 H), 5.60 (d, J = 8.0 Hz, 1 H), 7.02 (d, J = 2.0 Hz, 1 H), 7.12 (ddd, J = 7.8, 7.8, 1.0 Hz, 1 H), 7.18 (ddd, J = 7.5, 7.5, 1.0 Hz, 1 H), 7.35 (d, J = 8.0 Hz, 1 H), 7.58 (d, J = 7.8 Hz, 1 H), 8.38 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.7, 24.3, 28.3, 33.5, 46.7, 59.1, 79.9, 110.6, 111.3, 118.2, 119.5, 122.1, 122.8, 127.1, 136.1, 155.4, 173.6, 174.3 ppm. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 9 H), 2.88 (s, 3 H), 3.21 (dd, J = 15.2, 8.7 Hz, 1 H), 3.57 (dd, J = 14.8, 5.8 Hz, 1 H), 4.93 (dd, J = 8.0, 6.3 Hz, 1 H), 5.52 (d, J = 7.5 Hz, 1 H), 7.62 (d, J = 8.3 Hz, 1 H), 8.51 (br. s, 1 H) ppm.

***N-tert*-Butoxycarbonyl-(*S*)-alanyl-*N*-methyl-(*R*)-(2-chlorotryptophan) Methyl Ester (5):**[19] To a solution of dipeptide **3** (270 mg, 669 μmol) and dibenzoyl peroxide (75%, 11.0 mg, 34.0 μmol) in abs. CH_2Cl_2 (80 mL), *N*-Chlorosuccinimide (94 mg, 0.70 mmol) was added at –20 °C. The resulting reaction mixture was warmed to room temperature overnight, the solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate. The organic layer was washed with HCl (1 M), H_2O, satd. $NaHCO_3$ and brine, dried with Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (hexanes/ethyl acetate, 7:3) afforded chlorinated dipeptide **5** (183 mg, 418 μmol, 62%) as a colorless foam. R_f = 0.15 (hexanes/ethyl acetate, 7:3). $[\alpha]_D^{20}$ = +64.2 (c = 1.0, $CHCl_3$). 9:1 Mixture of rotamers. Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80 (d, J = 6.8 Hz, 3 H), 1.41 (s, 9 H), 2.84 (s, 3 H), 3.33 (dd, J = 15.3, 10.8 Hz, 1 H), 3.41 (dd, J = 15.5, 5.5 Hz, 1 H), 3.76 (s, 3 H), 4.43 (dq, J = 7.0, 7.0 Hz, 1 H), 5.18 (dd, J = 10.7, 5.1 Hz, 1 H), 5.44 (d, J = 8.0 Hz, 1 H), 7.10 (ddd, J = 7.8, 1.3 Hz, 1 H), 7.15 (ddd, J = 7.0, 7.0, 1.3 Hz, 1 H), 7.23 (d, J = 7.8 Hz, 1 H), 7.48 (d, J = 7.8 Hz, 1 H), 8.61 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.2, 23.4, 28.3, 33.6, 46.4, 52.4, 57.9, 79.4, 107.1, 110.5, 118.0, 120.3, 121.7, 122.5, 127.2, 134.4, 155.0, 170.9, 173.2 ppm. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 (s, 9 H), 2.97 (s, 3 H), 3.16 (dd, J = 14.8, 9.3 Hz, 1 H), 4.31 (m, 1 H), 4.79 (dd, J = 7.9, 6.4 Hz, 1 H), 5.31 (d, J = 7.3 Hz, 1 H), 8.56 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.9, 25.5, 29.7, 33.9, 49.2, 57.1, 120.7, 122.2 ppm. HRMS (CI): m/z calcd. $C_{21}H_{29}ClN_3O_5$ $[M + H]^+$ 438.1790; found 438.1823.

***N-tert*-Butoxycarbonyl-(*S*)-alanyl-*N*-methyl-(*R*)-2-chlorotryptophan (6):** To a solution of chlorinated dipeptide **5** (168 mg, 384 μmol) in MeOH (4 mL), NaOH (1 M, 57.0 μL, 57.0 μmol) was added at 0 °C. The solution was warmed to room temperature overnight, the solvent was removed and the residue was dissolved in H_2O. The aqueous solution was acidified to pH 3 with $KHSO_4$ (1 M) and extracted with ethyl acetate. The combined organic layers were washed with brine, dried with Na_2SO_4 and the solvents evaporated in vacuo to yield **6** (162 mg, 383 μmol, 99%) as a colorless foam. R_f = 0.31 [petroleum ether/ethyl acetate (1:1) + 1% AcOH]. $[\alpha]_D^{20}$ = +41.7 (c = 1.0, MeOH). 89:11 Mixture of rotamers. Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.82 (d, J = 6.8 Hz, 3 H), 1.42 (s, 9 H), 2.85 (s, 3 H), 3.41 (m, 2 H), 4.49 (dq, J = 7.5, 7.5 Hz, 1 H), 5.12 (dd, J = 9.9, 5.4 Hz, 1 H), 5.60 (d, J = 8.0 Hz, 1 H), 7.11 (ddd, J = 7.8, 7.8, 1.3 Hz, 1 H), 7.15 (ddd, J = 7.3, 7.3, 1.3 Hz, 1 H), 7.25 (d, J = 7.0 Hz, 1 H), 7.48 (d, J = 7.8 Hz, 1 H), 8.69 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8, 23.2, 28.3, 34.4, 46.5, 58.9, 79.8, 107.1, 110.6, 117.9, 120.3, 121.9, 122.5, 127.2, 134.4, 155.3, 173.6, 173.9 ppm. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 9 H), 2.92 (s, 3 H), 4.88 (dd, J = 8.9, 5.7 Hz, 1 H), 5.46 (d, J = 7.3 Hz, 1 H), 8.73 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.2, 24.1, 43.1, 60.4, 109.9, 110.5 ppm. HRMS (CI): m/z calcd. $C_{20}H_{27}ClN_3O_5$ $[M + H]^+$ 424.1634; found 424.1634. $C_{20}H_{26}ClN_3O_5$ (423.89): calcd. C 56.67, H 6.18, N 9.91; found C 56.47, H 6.18, N 9.66.

***N-tert*-Butoxycarbonyl-(*S*)-3-chloro-4-hydroxyphenylglycine (7):**[22] A suspension of (*S*)-4-hydroxyphenylglycine (4.87 g, 29.1 mmol) in AcOH (36 mL) was treated with SO_2Cl_2 (2.61 mL, 32.1 mmol), and stirred overnight at room temperature. The resulting hydrochloride was filtered and washed several times with AcOH and pentane. Lyophilization of the crude product resulted in the isolation of (*S*)-3-chloro-4-hydroxyphenylglycine·HCl (6.42 g, 27.0 mmol, 93%) as a colorless solid, m.p. 191–193 °C (decomposition). $[\alpha]_D^{20}$ = +128.7 (c = 1.0, MeOH). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 4.77 (s, 1 H), 7.07 (d, J = 8.3 Hz, 1 H), 7.21 (dd, J = 8.4, 2.1 Hz, 1 H), 7.46 (d, J = 2.0 Hz, 1 H), 8.79 (br. s, 3 H, NH_3), 10.99 (br. s, 1 H, COOH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 55.2, 116.7, 119.6, 125.7, 127.9, 129.5, 153.8, 169.7 ppm.

To a solution of (*S*)-3-chloro-4-hydroxyphenylglycine·HCl (6.36 g, 26.7 mmol) and $NaHCO_3$ (4.49 g, 53.4 mmol) in H_2O (75 mL) was added a solution of Boc_2O (6.41 g, 29.4 mmol) in THF (75 mL of THF) at 0 °C, and the reaction mixture was warmed to room temperature overnight. After removal of the organic solvent under reduced pressure, the aqueous layer was acidified with HCl (6 M) to pH 2–3 and extracted with ethyl acetate. The combined organic layers were further washed with brine, dried with Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography [hexanes/ethyl acetate (1:1) + 1% AcOH] resulted in isolation of Boc-protected amino acid **7** (7.76 g, 25.7 mmol, 96%) as a colorless solid, m.p. 88–91 °C. R_f = 0.36 [hexanes/ethyl acetate (1:1) + 1% AcOH]. $[\alpha]_D^{20}$ = +115.1 (c = 1.3, MeOH). 7:3 Mixture of rotamers. Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (s, 9 H), 5.04 (d, J = 5.3 Hz, 1 H), 6.98 (d, J = 8.5 Hz, 1 H), 7.23 (m, 1 H), 7.41 (d, J = 1.8 Hz, 1 H), 8.10 (d, J = 5.3 Hz, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.0, 57.8, 82.1, 116.2, 119.9, 127.3, 127.7, 131.5, 151.1, 156.9, 173.1 ppm. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (s, 9 H), 5.25 (d, J = 6.5 Hz, 1 H), 5.59 (br. s, 1 H, NH), 7.37 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.2, 56.5, 116.7, 120.3, 154.9 ppm. HPLC (hexane/*i*PrOH, 7:3, 1 mL/min): t_R = 5.87 min [(*S*)-**7**], t_R = 7.20 min [(*R*)-**7**].

***N-tert*-Butoxycarbonyl-(*S*)-3-chloro-4-(*tert*-butyldimethylsilyloxy)-phenylglycine (8a):**[22] To a solution of Boc-protected amino acid **7** (2.59 g, 8.58 mmol) in abs. DMF (40 mL) $NaHCO_3$ (0.72 g, 8.58 mmol) and benzyl bromide (1.61 g, 9.44 mmol) were added at 0 °C. After being warmed to room temperature overnight, the mix-

ture was diluted with H_2O and extracted with ethyl acetate. The combined organic layers were washed with H_2O and brine, dried with Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (hexanes/ethyl acetate, 8:2) gave rise to *N*-*tert*-butoxycarbonyl-(*S*)-3-chloro-4-hydroxyphenylglycine benzyl ester (2.57 g, 6.55 mmol, 76%) as a colorless oil. R_f = 0.12 (hexanes/ethyl acetate, 8:2). $[\alpha]_D^{20}$ = +54.4 (*c* = 1.6, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.43 (s, 9 H), 5.16 (s, 2 H), 5.27 (d, *J* = 6.8 Hz, 1 H), 5.60 (d, *J* = 6.0 Hz, 1 H, NH), 5.92 (s, 1 H, OH), 6.91 (d, *J* = 8.5 Hz, 1 H), 7.13 (dd, *J* = 8.5, 2.0 Hz, 1 H), 7.22 (m, 2 H), 7.29–7.32 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.3, 56.7, 67.5, 80.4, 116.5, 120.2, 127.7, 127.8, 128.0, 128.4, 128.5, 130.0, 134.9, 151.6, 154.7, 170.6 ppm. HPLC (hexane/*i*PrOH, 7:3, 1 mL/min): t_R = 6.91 min [(*S*)-isomer], t_R = 10.84 min [(*R*)-isomer].

To a solution of *N*-*tert*-butoxycarbonyl-(*S*)-3-chloro-4-hydroxyphenylglycine benzyl ester (2.66 g, 6.79 mmol) in abs. DMF (15 mL), TBSCl (3.07 g, 20.4 mmol) and imidazole (2.78 g, 40.7 mmol) were added at 0 °C, and the mixture was warmed to room temperature overnight. The solution was diluted with ethyl acetate and washed with HCl (1 M), satd. $NaHCO_3$ and brine, dried with Na_2SO_4 and the solvents evaporated in vacuo. Purification by flash chromatography (hexanes/ethyl acetate, 9:1) provided *N*-*tert*-butoxycarbonyl-(*S*)-3-chloro-4-(*tert*-butyldimethylsilyloxy)phenylglycine benzyl ester (3.40 g, 6.72 mmol, 99%) as a colorless oil. R_f = 0.29 (hexanes/ethyl acetate, 9:1). $[\alpha]_D^{20}$ = +48.4 (*c* = 2.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.22 (s, 6 H), 1.03 (s, 9 H), 1.43 (s, 9 H), 5.14 (d, *J* = 11.5 Hz, 1 H), 5.18 (d, *J* = 12.5 Hz, 1 H), 5.28 (d, *J* = 7.0 Hz, 1 H), 5.52 (d, *J* = 6.5 Hz, 1 H, NH), 6.82 (d, *J* = 8.3 Hz, 1 H), 7.09 (dd, *J* = 8.3, 2.3 Hz, 1 H), 7.21 (m, 2 H), 7.29–7.33 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.4, 18.3, 25.6, 28.3, 56.7, 67.4, 80.3, 120.8, 125.9, 126.4, 127.9, 128.3, 128.5, 128.9, 130.6, 135.1, 151.7, 154.7, 170.7 ppm. HPLC [hexane/*i*PrOH (9:1) for 15 min, then in 15 min to 8:2, 1 mL/min]: t_R = 9.75 min [(*S*)-isomer], t_R = 20.63 min [(*R*)-isomer].

A mixture of *N*-*tert*-butoxycarbonyl-(*S*)-3-chloro-4-hydroxyphenylglycine benzyl ester (6.03 g, 11.9 mmol) and Pd/C (10%, 0.63 g) in abs. MeOH (60 mL) was stirred under a hydrogen atmosphere (1 atm, room temp.) until complete conversion. Filtration over Celite and removal of the solvent under reduced pressure resulted in the isolation of *N*,*O*-protected amino acid **8a** (4.80 g, 11.5 mmol, 97%) as a colorless solid, m.p. 68–70 °C. R_f = 0.49 [petroleum ether/ethyl acetate (1:1) + 1% AcOH]. $[\alpha]_D^{20}$ = +90.2 (*c* = 3.9, $CHCl_3$). 82:18 Mixture of rotamers. Major rotamer: ^1H NMR (400 MHz, $CDCl_3$): δ = 0.22 (s, 6 H), 1.03 (s, 9 H), 1.25 (s, 9 H), 5.03 (d, *J* = 5.0 Hz, 1 H), 6.85 (d, *J* = 8.5 Hz, 1 H), 7.20 (dd, *J* = 8.5, 1.8 Hz, 1 H), 7.43 (d, *J* = 1.8 Hz, 1 H), 8.12 (d, *J* = 4.3 Hz, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.4, 18.3, 25.6, 28.0, 57.8, 81.9, 120.6, 125.5, 126.2, 129.2, 132.2, 151.3, 156.9, 173.1 ppm. Minor rotamer (selected signals): ^1H NMR (400 MHz, $CDCl_3$): δ = 1.43 (s, 9 H), 5.25 (d, *J* = 5.5 Hz, 1 H), 5.51 (br. s, 1 H), 6.82 (d, *J* = 8.3 Hz, 1 H), 7.15 (m, 1 H), 7.38 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.3, 80.6, 126.5, 128.9, 151.9 ppm.

***N*-*tert*-Butoxycarbonyl-(*S*)-3-bromo-4-(*tert*-butyldimethylsilyloxyphenyl)glycine (8b):** To a solution of **10** (5.24 g, 10.5 mmol, 62% *ee*) in abs. THF (52 mL) $Pd(PPh_3)_4$ (0.40 g, 0.34 mmol) and morpholine (1.82 mL, 20.9 mmol) were added. The reaction mixture was stirred for 2 h, diluted with ethyl acetate, washed twice with HCl (1 M) and brine, dried with Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography [petroleum ether/ethyl acetate (8:2) + 1% AcOH] gave rise to **8b** (4.51 g, 9.80 mmol, 94%, 62% *ee*) as a colorless solid, m.p. 70–72 °C. R_f = 0.20 [petroleum ether/ethyl acetate (8:2) + 1% AcOH]. 8:2 Mixture of rotamers. Major rotamer: ^1H NMR (400 MHz, $CDCl_3$): δ = 0.24 (s, 6 H), 1.04 (s, 9 H), 1.26 (s, 9 H), 5.02 (d, *J* = 5.0 Hz, 1 H), 6.84 (d, *J* = 8.5 Hz, 1 H), 7.24 (m, 1 H), 7.59 (d, *J* = 1.8 Hz, 1 H), 8.08 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.2, 18.3, 25.7, 28.4, 57.7, 81.9, 115.2, 120.1, 126.9, 132.3, 132.4, 152.4, 156.9, 173.1 ppm. Minor rotamer (selected signals): ^1H NMR (400 MHz, $CDCl_3$): δ = 1.44 (s, 9 H), 5.25 (d, *J* = 5.0 Hz, 1 H), 5.48 (s, 1 H, NH), 7.19 (m, 1 H), 7.55 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.3, 120.2, 127.3, 132.0 ppm. HRMS (CI): *m*/*z* calcd. $C_{19}H_{30}BrNO_5Si$ $[M]^+$ 459.1071; found 459.1051. $C_{19}H_{30}BrNO_5Si$ (460.44): calcd. C 49.56, H 6.57, N 3.04; found C 50.09, H 6.59, N 3.07.

***N*-*tert*-Butoxycarbonyl-(*S*)-3-bromo-4-hydroxyphenylglycine Allyl Ester (9):** To a suspension of (*S*)-4-hydroxyphenylglycine (4.83 g, 28.9 mmol) in AcOH (13 mL), HBr (33% in AcOH, 14.5 mL, 84.0 mmol) and a solution of Br_2 (1.64 mL, 31.8 mmol) in AcOH (10 mL) were successively added over 1 h. The resulting mixture was stirred for 24 h at room temperature and cooled to 0 °C. The precipitate was filtered and washed several times with AcOH and diethyl ether to obtain (*S*)-3-bromo-4-hydroxyphenylglycine·HBr[23] (8.24 g, 25.2 mmol, 87%) as a pale yellow solid, m.p. 219–220 °C. $[\alpha]_D^{20}$ = +106.6 (*c* = 1.0, MeOH). ^1H NMR (400 MHz, $[D_4]$MeOD): δ = 5.01 (s, 1 H), 6.97 (d, *J* = 8.5 Hz, 1 H), 7.29 (dd, *J* = 8.3, 2.3 Hz, 1 H), 7.62 (d, *J* = 2.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $[D_4]$MeOD): δ = 56.5, 111.4, 117.7, 125.9, 129.7, 134.1, 157.1, 170.7 ppm. HRMS (CI): *m*/*z* calcd. $C_8H_8BrNO_3$ $[M - Br]^-$ 245.9760; found 245.9771. $C_8H_9Br_2NO_3$ (326.97): calcd. C 29.39, H 2.77, N 4.28; found C 29.24, H 2.36, N 4.24.

To a solution of (*S*)-3-bromo-4-hydroxyphenylglycine·HBr (5.54 g, 16.9 mmol) in NaOH (1 M, 65 mL) and dioxane (30 mL) Boc_2O (4.44 g, 20.3 mmol) was added at 0 °C, and the reaction mixture was warmed to room temperature overnight. After removal of the organic solvent under reduced pressure, the aqueous layer was acidified with HCl (6 M) to pH 2–3 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated in vacuo to obtain *N*-*tert*-butoxycarbonyl-(*S*)-3-bromo-4-hydroxyphenylglycine[23] (5.79 g, 16.7 mmol, 99%, 62% *ee*) as a colorless solid, m.p. 88–90 °C. R_f = 0.36 [petroleum ether/ethyl acetate (1:1) + 1% AcOH]. 75:25 Mixture of rotamers. Major rotamer: ^1H NMR (400 MHz, $CDCl_3$): δ = 1.26 (s, 9 H), 5.03 (d, *J* = 5.0 Hz, 1 H), 6.96 (d, *J* = 8.3 Hz, 1 H), 7.26 (m, 1 H), 7.54 (s, 1 H), 8.01 (d, *J* = 4.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.0, 57.7, 82.1, 110.1, 116.0, 127.9, 130.7, 131.7, 152.1, 156.9, 173.2 ppm. Minor rotamer (selected signals): ^1H NMR (400 MHz, $CDCl_3$): δ = 1.42 (s, 9 H), 5.24 (d, *J* = 5.5 Hz, 1 H), 5.66 (d, *J* = 5.5 Hz, 1 H, NH), 6.92 (m, 1 H), 7.78 (d, *J* = 7.8 Hz, 1 H), 7.48 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.3, 56.4, 80.9, 116.3, 129.9, 174.5 ppm. HRMS (CI): *m*/*z* calcd. $C_{13}H_{17}BrNO_5$ $[M + H]^+$ 346.0285; found 346.0263. $C_{13}H_{16}BrNO_5$ (346.17): calcd. C 45.10, H 4.66, N 4.05; found C 45.06, H 4.63, N 3.84.

According to *N*-Boc-(*S*)-3-chloro-4-hydroxyphenylglycine benzyl ester, allylic ester **9** was prepared from *N*-*tert*-butoxycarbonyl-(*S*)-3-bromo-4-hydroxyphenylglycine (2.87 g, 8.29 mmol, 62% *ee*), K_2CO_3 (1.26 g, 9.12 mmol), and allyl bromide (0.93 mL, 10.8 mmol) in abs. DMF (83 mL). Purification by flash chromatography (petroleum ether/ethyl acetate, 7:3) gave rise to **9** (1.87 g, 4.84 mmol, 58%, 62% *ee*) as a colorless oil. R_f = 0.36 (petroleum ether/ethyl acetate, 7:3). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.43 (s, 9 H), 4.62 (m, 2 H), 5.19–5.25 (m, 3 H), 5.58 (d, *J* = 5.5 Hz, 1 H, NH), 5.78–5.87 (m, 2 H), 6.95 (d, *J* = 8.3 Hz, 1 H), 7.21 (dd, *J* =

8.3, 1.8 Hz, 1 H), 7.48 (d, J = 2.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.3, 56.6, 66.3, 80.4, 110.4, 116.4, 118.8, 127.9, 130.5, 130.7, 131.2, 152.5, 154.7, 170.5 ppm. HRMS (CI): m/z calcd. $C_{16}H_{21}BrNO_5$ $[M + H]^+$ 386.0598; found 386.0638. $C_{16}H_{20}BrNO_5$ (386.24): calcd. C 49.75, H 5.22, N 3.63; found C 49.64, H 5.42, N 3.72.

***N*-*tert*-Butoxycarbonyl-(*S*)-3-bromo-4-(*tert*-butyldimethylsilyloxy)-phenylglycine Allyl Ester (10):** In analogy to *N*-Boc-(*S*)-3-chloro-4-(*tert*-butyldimethylsilyloxy)phenylglycine benzyl ester *N*,*O*-protected amino acid **10** was obtained from allylic ester **9** (4.32 g, 11.2 mmol, 62% *ee*), TBSCl (1.85 g, 12.3 mmol) and imidazole (1.52 g, 22.4 mmol) in abs. DMF (55 mL). Purification by flash chromatography (petroleum ether/ethyl acetate, 9:1) provided **10** (5.37 g, 10.7 mmol, 96%, 62% *ee*) as a colorless oil. R_f = 0.33 (petroleum ether/ethyl acetate, 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.24 (s, 6 H), 1.03 (s, 9 H), 1.43 (s, 9 H), 4.62 (d, J = 5.5 Hz, 2 H), 5.17–5.22 (m, 2 H), 5.24 (d, J = 7.0 Hz, 1 H), 5.51 (d, J = 6.0 Hz, 1 H, NH), 5.83 (ddt, J = 17.3, 10.0, 5.8 Hz, 1 H), 6.82 (d, J = 8.3 Hz, 1 H), 7.17 (dd, J = 8.4, 1.9 Hz, 1 H), 7.52 (d, J = 2.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.3, 18.3, 25.7, 28.3, 56.6, 66.2, 80.3, 115.6, 118.6, 120.2, 127.2, 130.9, 131.3, 131.9, 152.8, 154.7, 170.6 ppm. HRMS (CI): m/z calcd. $C_{22}H_{34}BrNO_5Si$ $[M]^+$ 499.1384; found 499.1366. $C_{22}H_{34}BrNO_5Si$ (500.50): calcd. C 52.79, H 6.85, N 2.80; found C 53.14, H 6.85, N 2.99.

(*S*)-*tert*-Butyl-{1-[3-chloro-4-(*tert*-butyldimethylsilyloxy)phenyl]-3-diazo-2-oxopropyl}carbamate (11a): To a mixture of KOH (40%, 20 mL) and diethyl ether (90 mL) 1-methyl-1-nitrosourea (1.51 g, 14.7 mmol) was added in several portions at –10 °C (internal temperature should not increase above –5 °C). The reaction mixture was cooled to –78 °C, the organic layer was decanted and washed with H_2O and brine.

To a solution of *N*,*O*-protected amino acid **8a** (3.05 g, 7.34 mmol) in abs. THF (120 mL) Et_3N (1.03 mL, 7.41 mmol) and ClCOOEt (0.71 mL, 7.41 mmol) were added at –20 °C. After 20 min at this temperature, the suspension was cooled to –78 °C and freshly prepared diazomethane was added. The reaction mixture was warmed to room temperature overnight. After addition of H_2O, the layers were separated and extracted with ethyl acetate. The combined organic layers were further washed with satd. $NaHCO_3$, H_2O and brine, dried with Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (hexanes/ethyl acetate, 9:1) resulted in isolation of **11a** (2.64 g, 5.99 mmol, 82%) as a yellow solid, m.p. 51–53 °C. R_f = 0.23 (petroleum ether/ethyl acetate, 8:2). $[\alpha]_D^{20}$ = +183.4 (c = 0.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.21 (s, 6 H), 1.01 (s, 9 H), 1.41 (s, 9 H), 5.08 (s, 1 H), 5.24 (s, 1 H), 5.82 (d, J = 5.3 Hz, 1 H), 6.84 (d, J = 8.3 Hz, 1 H), 7.07 (d, J = 7.0 Hz, 1 H), 7.29 (d, J = 2.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.4, 18.3, 25.6, 28.3, 54.7, 60.7, 80.2, 120.9, 126.2, 126.8, 129.4, 131.1, 151.8, 154.9, 190.4 ppm. HPLC (hexane/*i*PrOH, 8:2, 1 mL/min): t_R = 8.57 min [(*S*)-**11a**], t_R = 12.55 min [(*R*)-**11a**]. HRMS (CI): m/z calcd. $C_{20}H_{30}ClN_3O_4Si$ $[M]^+$ 439.1689; found 439.1651.

(*S*)-*tert*-Butyl-{1-[3-bromo-4-(*tert*-butyldimethylsilyloxy)phenyl]-3-diazo-2-oxopropyl}carbamate (11b): The diazo ketone **11b** was prepared according to **11a** from KOH (40%, 15 mL), diethyl ether (50 mL), 1-methyl-1-nitrosourea (0.96 g, 9.30 mmol), *N*,*O*-protected amino acid **8b** (2.14 g, 4.65 mmol, 62% *ee*), Et_3N (0.71 mL, 5.11 mmol) and ClCOOEt (0.49 mL, 5.11 mmol mL) in abs. THF (60 mL). The reaction mixture was warmed to –15 °C and the excess of diazomethane was destroyed by addition of AcOH. Purification by flash chromatography (petroleum ether/ethyl acetate, 8:2) provided **11b** (1.84 g, 3.80 mmol, 82%, 62% *ee*) as a yellow solid. R_f = 0.24 (petroleum ether/ethyl acetate, 8:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.24 (s, 6 H), 1.34 (s, 9 H), 1.41 (s, 9 H), 5.07 (br. s, 1 H), 5.24 (br. s, 1 H), 5.81 (br. s, 1 H, NH), 6.83 (d, J = 8.3 Hz, 1 H), 7.12 (d, J = 7.3 Hz, 1 H), 7.46 (d, J = 2.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.3, 18.3, 25.6, 28.3, 54.7, 60.6, 80.1, 115.9, 120.3, 127.6, 131.4, 132.4, 152.8, 154.9, 190.4 ppm. HPLC (hexane/*i*PrOH, 8:2, 1 mL/min): t_R = 9.41 min [(*S*)-**11b**], t_R = 14.77 min [(*R*)-**11b**]. HRMS (CI): m/z calcd. $C_{20}H_{31}BrN_3O_4Si$ $[M + H]^+$ 484.1262; found 484.1212.

***N*-*tert*-Butoxycarbonyl-(*R*)-3-chloro-4-(*tert*-butyldimethylsilyloxy)-β-phenylalanine (12a):** To a solution of diazo ketone **11a** (0.97 g, 2.21 mmol) in ethyl acetate (58 mL) were added BzOAg (25.0 mg, 0.11 mmol) and SiO_2 (9.70 g).[25] After shaking for 3 h at 45 °C, the silica gel was filtered over Celite. The organic layer was washed with HCl (1 M) and brine, dried with Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography [petroleum ether/ethyl acetate (8:2) + 1% AcOH] gave rise to **12a** (0.75 g, 1.75 mmol, 79%) as a colorless solid, m.p. 41–42 °C. R_f = 0.27 [petroleum ether/ethyl acetate (8:2) + 1% AcOH]. $[\alpha]_D^{20}$ = +26.9 (c = 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.21 (s, 6 H), 1.02 (s, 9 H), 1.40 (s, 9 H), 2.80 (br. s, 2 H), 5.01 (s, 1 H), 5.40 (s, 0.5 H, NH), 6.49 (s, 0.5 H, NH), 6.83 (d, J = 8.5 Hz, 1 H), 7.05 (dd, J = 8.5, 2.3 Hz, 1 H), 7.28 (d, J = 2.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.4, 18.3, 25.6, 28.3, 40.4, 50.0, 80.1, 120.7, 125.4, 125.7, 128.1, 134.8, 150.9, 155.0, 175.3 ppm. HPLC (hexane/*i*PrOH, 8:2, 1 mL/min): t_R = 5.96 min [(*R*)-**12a**], t_R = 14.67 min [(*S*)-**12a**]. HRMS (CI): m/z calcd. $C_{20}H_{33}ClNO_5Si$ $[M + H]^+$ 430.1811; found 430.1796. $C_{20}H_{32}ClNO_5Si$ (430.01): calcd. C 55.86, H 7.50, N 3.26; found C 56.08, H 7.23, N 3.65.

***N*-*tert*-Butoxycarbonyl-(*R*)-3-chloro-4-(*tert*-butyldimethylsilyloxy)-β-phenylalanine-{allyl [(*E*)-4-methylhept-4-enoate]-7-yl} Ester (13a). Method a:** According to dipeptide **3**, ester **13a** was prepared from β-amino acid **12a** (276 mg, 0.64 mmol), ω-hydroxy ester **2** (140 mg, 0.71 mmol), 4-(dimethylamino)pyridine (DMAP; 15.0 mg, 0.12 mmol) and DCC (146 mg, 0.71 mmol) in abs. diethyl ether (4.3 mL). Purification by flash chromatography (petroleum ether/ethyl acetate, 8:2) provided ester **13a** (345 mg, 0.57 mmol, 88%) as a colorless oil.

Method b. To a solution of diazo ketone **11a** (1.99 g, 4.52 mmol) and ω-hydroxy ester **2** (1.79 g, 9.04 mmol) in abs. THF (4.5 mL) solution of AgOBz (114 mg, 0.50 mmol) in Et_3N (1.80 mL, 12.9 mmol) was added in the dark at –25 °C. The reaction mixture was warmed to room temperature overnight. The precipitate was filtered, diluted with ethyl acetate and the organic layer was washed with $Na_2S_2O_3$ (1 M), satd. $NaHCO_3$, H_2O, satd. NH_4Cl, brine and dried with Na_2SO_4. Removal of the solvent under reduced pressure and purification by flash chromatography (hexanes/ethyl acetate, 8:2) resulted in the isolation of **13a** (2.25 g, 3.69 mmol, 82%) as a colorless oil. R_f = 0.26 (petroleum ether/ethyl acetate, 8:2). $[\alpha]_D^{20}$ = +16.9 (c = 1.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.20 (s, 6 H), 1.01 (s, 9 H), 1.42 (s, 9 H), 1.61 (s, 3 H), 2.24 (dt, J = 7.2, 7.2 Hz, 2 H), 2.32 (m, 2 H), 2.43 (m, 2 H), 2.74 (dd, J = 15.6, 5.8 Hz, 1 H), 2.82 (dd, J = 15.6, 6.5 Hz, 1 H), 3.97 (td, J = 7.3, 1.3 Hz, 2 H), 4.56 (ddd, J = 5.8, 1.3, 1.3 Hz, 2 H), 5.00 (br. s, 1 H), 5.08 (tq, J = 7.0, 1.0 Hz, 1 H), 5.22 (ddt, J = 10.3, 1.3, 1.3 Hz, 1 H), 5.30 (ddt, J = 17.3, 1.5, 1.5 Hz, 1 H), 5.47 (br. s, 1 H), 5.91 (ddt, J = 17.1, 10.3, 5.8 Hz, 1 H), 6.82 (d, J = 8.3 Hz, 1 H), 7.04 (dd, J = 8.5, 2.3 Hz, 1 H), 7.27 (d, J = 2.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.4, 16.0, 18.3, 25.6, 27.3, 28.3, 32.9, 34.5, 40.8, 50.4, 64.2, 65.0, 79.8, 118.2, 119.8, 120.6, 125.4, 125.6, 128.0, 132.2, 135.2, 136.7, 150.8, 154.9, 170.7, 172.8 ppm. HPLC [hexane/*i*PrOH (8:2) for 15 min, then in 15 min to 7:3, 1 mL/min]: t_R =

9.48 min [(*R*)-**13a**], t_R = 23.28 min [(*S*)-**13a**]. HPLC/MS (H_2O/ACN, 1:9, 10 min, 0.6 mL/min): t_R = 4.12 min (*m*/*z* calcd. $C_{31}H_{48}ClNO_7Si + Na^+$ 632; found 632). HRMS (CI): *m*/*z* calcd. $C_{31}H_{49}ClNO_7Si$ $[M + H]^+$ 610.2961; found 610.2968. $C_{31}H_{48}ClNO_7Si$ (610.25): calcd. C 61.01, H 7.93, N 2.30; found C 60.65, H 8.06, N 2.77.

***N*-*tert*-Butoxycarbonyl-(*R*)-3-bromo-4-(*tert*-butyldimethylsilyloxy)-β-phenylalanine-{allyl [(*E*)-4-methylhept-4-enoate]-7-yl} Ester (13b):** The ester **13b** was prepared in analogy to ester **13a** from diazo ketone **11b** (310 mg, 0.64 mmol), ω-hydroxy ester **2** (270 mg, 1.36 mmol) in abs. THF (1.5 mL) and AgOBz (16.0 mg, 0.07 mmol) in Et_3N (0.26 mL, 1.86 mmol). Purification by flash chromatography (petroleum ether/ethyl acetate, 8:2) provided ester **13b** (266 mg, 0.41 mmol, 64%) as a colorless oil. R_f = 0.31 (petroleum ether/ethyl acetate, 8:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.23 (s, 6 H), 1.02 (s, 9 H), 1.42 (s, 9 H), 1.61 (s, 3 H), 2.24 (dt, *J* = 7.0 Hz, 2 H), 2.32 (m, 2 H), 2.44 (m, 2 H), 2.74 (dd, *J* = 15.6, 6.0 Hz, 1 H), 2.81 (dd, *J* = 15.8, 6.3 Hz, 1 H), 3.97 (td, *J* = 7.0, 1.5 Hz, 2 H), 4.56 (ddd, *J* = 5.8, 1.3, 1.3 Hz, 2 H), 4.99 (br. s, 1 H), 5.08 (tq, *J* = 7.0, 1.0 Hz, 1 H), 5.23 (ddt, *J* = 10.3, 1.3, 1.3 Hz, 1 H), 5.30 (ddt, *J* = 17.3, 1.5, 1.5 Hz, 1 H), 5.45 (br. s, 1 H, NH), 5.91 (ddt, *J* = 17.1, 10.3, 5.8 Hz, 1 H), 6.80 (d, *J* = 8.3 Hz, 1 H), 7.09 (dd, *J* = 8.5, 2.3 Hz, 1 H), 7.44 (d, *J* = 2.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.3, 16.0, 18.3, 25.7, 27.3, 28.3, 32.9, 34.5, 40.8, 50.2, 64.2, 65.0, 79.8, 115.4, 118.2, 119.8, 120.0, 126.2, 131.1, 132.2, 132.2, 136.7, 151.8, 154.9, 170.7, 172.8 ppm. HPLC [hexane/*i*PrOH (8:2) for 15 min, then in 15 min to 7:3, 1 mL/min]: t_R = 9.80 min [(*R*)-**13b**], t_R = 25.76 min [(*S*)-**13b**]. HRMS (CI): *m*/*z* calcd. $C_{31}H_{49}BrNO_7Si$ $[M + H]^+$ 654.2456; found 654.2462. $C_{31}H_{48}BrNO_7Si$ (654.70): calcd. C 56.87, H 7.39, N 2.14; found C 56.50, H 6.64, N 2.55.

***N*-*tert*-Butoxycarbonyl-(*S*)-alanyl-*N*-methyl-(*R*)-2-chlorotryptophanyl-(*R*)-3-chloro-4-(*tert*-butyldimethylsilyloxy)-β-phenylalanine-{allyl [(*E*)-4-methylhept-4-enoate]-7-yl} Ester (14a):** A solution of β-tyrosine ester **13a** (0.26 g, 0.43 mmol) in abs. CH_2Cl_2 (3 mL) was treated with trifluoroacetic acid (TFA; 1.32 mL, 17.1 mmol) at –20 °C and was stirred for 16 h at this temperature. The reaction mixture was poured into satd. $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layer was further washed with brine, dried with Na_2SO_4 and concentrated in vacuo. To a solution of the resulted crude amine in abs. CH_2Cl_2 (1.2 mL) chlorinated dipeptide **6** (0.22 g, 0.51 mmol), *i*Pr_2NEt (90 µL, 0.51 mmol) and COMU® (1-Cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate;[27] 0.22 g, 0.51 mmol) were added at 0 °C. The mixture was warmed to room temperature overnight, concentrated to dryness and the residue was dissolved in ethyl acetate. The organic layer was further washed with $KHSO_4$ (1 M), H_2O, satd. $NaHCO_3$ and brine, dried with Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (petroleum ether/ethyl acetate, 7:3) resulted in the isolation of **14a** (0.36 g, 0.39 mmol, 91%) as a pale yellow foam. R_f = 0.13 (petroleum ether/ethyl acetate, 7:3). $[\alpha]_D^{20}$ = +9.5 (*c* = 2.6, $CHCl_3$). 91:9 Mixture of diastereomers. Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.21 (s, 6 H), 0.68 (d, *J* = 6.8 Hz, 3 H), 1.01 (s, 9 H), 1.36 (s, 9 H), 1.61 (s, 3 H), 2.24 (td, *J* = 7.0 Hz, 2 H), 2.31 (m, 2 H), 2.43 (m, 2 H), 2.74 (dd, *J* = 15.8, 6.0 Hz, 1 H), 2.86 (dd, *J* = 15.8, 8.0 Hz, 1 H), 2.95 (s, 3 H), 3.21 (dd, *J* = 15.2, 10.9 Hz, 1 H), 3.40 (dd, *J* = 15.3, 5.5 Hz, 1 H), 3.97 (t, *J* = 7.2 Hz, 2 H), 4.27 (dq, *J* = 6.8 Hz, 1 H), 4.56 (ddd, *J* = 5.8, 1.5, 1.5 Hz, 2 H), 5.07–5.11 (m, 2 H), 5.22 (ddt, *J* = 10.3, 1.3, 1.3 Hz, 1 H), 5.30 (ddt, *J* = 17.3, 1.5, 1.5 Hz, 1 H), 5.36 (ddd, *J* = 6.5, 6.5, 6.5 Hz, 1 H), 5.65 (dd, *J* = 10.5, 5.5 Hz, 1 H), 5.90 (ddt, *J* = 17.3, 10.5, 5.5 Hz, 1 H), 6.77 (d, *J* = 8.3 Hz, 1 H), 6.96–7.13 (m, 4 H), 7.19–7.22 (m, 2 H), 7.49 (d, *J* = 7.5 Hz, 1 H), 8.40 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.4 16.0, 16.6, 18.3, 22.3, 25.6, 27.3, 28.3, 31.5, 32.9, 34.5, 40.3, 46.4, 49.1, 56.2, 64.1, 65.0, 79.7, 107.3, 110.4, 118.2, 118.3, 119.8, 120.2, 120.6, 121.5, 122.3, 125.6, 125.7, 127.3, 128.2, 132.2, 134.4, 134.6, 136.6, 150.9, 155.6, 169.3, 170.4, 172.9, 174.1 ppm. Minor diastereomer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.19 (s, 6 H), 1.01 (s, 9 H), 1.38 (s, 9 H), 1.62 (s, 3 H), 2.72 (s, 3 H), 3.32 (dd, *J* = 15.4, 3.6 Hz, 1 H), 3.82 (t, *J* = 7.2 Hz, 2 H), 4.03 (m, 1 H), 4.85 (d, *J* = 6.3 Hz, 2 H), 4.94 (dd, *J* = 10.9, 3.4 Hz, 1 H), 5.45 (m, 1 H), 5.90 (ddt, *J* = 17.3, 10.5, 5.5 Hz, 1 H), 6.78 (d, *J* = 8.5 Hz, 1 H), 7.29 (d, *J* = 2.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 64.1 ppm. HPLC [hexane/*i*PrOH (6:4) for 15 min, then in 15 min to 1:1, 1 mL/min]: t_R = 17.92 min [(*R*/*S*)-**14a**]. HPLC/MS (H_2O/ACN, 1:9, 10 min, 0.6 mL/min): t_R = 3.82 min (*m*/*z* calcd. $[C_{46}H_{64}Cl_2N_4O_9Si + Na]^+$ 937; found 937). HRMS (CI): *m*/*z* calcd. $C_{46}H_{65}Cl_2N_4O_9Si$ $[M + H]^+$ 915.3892; found 915.3930.

***N*-*tert*-Butoxycarbonyl-(*S*)-alanyl-*N*-methyl-(*R*)-tryptophanyl-(*R*)-3-chloro-4-(*tert*-butyldimethylsilyloxy)-β-phenylalanine-{allyl [(*E*)-4-methylhept-4-enoate]-7-yl} Ester (15a):** Tripeptide **15a** was prepared according **14a** from β-tyrosine ester **13a** (0.42 g, 0.69 mmol), TFA (1.01 mL, 13.7 mmol) in abs. CH_2Cl_2 (5 mL) and dipeptide **4** (0.32 g, 0.82 mmol), *i*Pr_2NEt (0.22 mL, 1.27 mmol) and COMU® (0.35 g, 0.83 mmol) in abs. CH_2Cl_2 (2 mL). Purification by flash chromatography (petroleum ether/ethyl acetate, 6:4) provided **15a** (0.44 g, 0.50 mmol, 72%) as a pale yellow foam. R_f = 0.33 (petroleum ether/ethyl acetate, 1:1). 73:27 Mixture of diastereomers. Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.20 (s, 6 H), 0.94 (d, *J* = 6.5 Hz, 3 H), 1.01 (s, 9 H), 1.40 (s, 9 H), 1.61 (s, 3 H), 2.23 (m, 2 H), 2.31 (m, 2 H), 2.43 (m, 2 H), 2.72 (dd, *J* = 16.0, 7.3 Hz, 1 H), 2.85 (dd, *J* = 15.6, 8.0 Hz, 1 H), 2.92 (s, 3 H), 3.21 (dd, *J* = 15.8, 10.3 Hz, 1 H), 3.46 (dd, *J* = 15.6, 5.8 Hz, 1 H), 3.97 (t, *J* = 7.0 Hz, 2 H), 4.38 (dq, *J* = 6.8, 6.8 Hz, 1 H), 4.56 (ddd, *J* = 5.5, 1.3, 1.3 Hz, 2 H), 5.08 (t, *J* = 7.3 Hz, 1 H), 5.21–5.34 (m, 4 H), 5.60 (m, 1 H), 5.90 (ddt, *J* = 17.1, 10.5, 5.8 Hz, 1 H), 6.77 (d, *J* = 8.3 Hz, 1 H), 6.96–7.21 (m, 6 H), 7.32 (d, *J* = 7.8 Hz, 1 H), 7.59 (d, *J* = 7.8 Hz, 1 H), 8.20 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.3, 16.1 17.0, 18.3, 23.2, 25.6, 27.4, 28.3, 30.9, 32.9, 34.5, 40.3, 46.6, 49.1, 56.7, 64.2, 65.1, 79.9, 111.0, 111.1, 118.2, 118.6, 119.4, 119.8, 120.6, 122.1, 122.1, 125.6, 125.7, 127.4, 128.2, 132.2, 134.7, 136.1, 136.6, 150.8, 155.7, 169.4, 170.5, 172.8, 174.3 ppm. Minor diastereomer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (s, 9 H), 1.44 (s, 9 H), 1.59 (s, 3 H), 2.77 (s, 3 H), 3.14 (m, 1 H), 3.40 (m, 1 H), 3.91 (t, *J* = 7.3 Hz, 2 H), 6.81 (d, *J* = 8.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.3, 28.4, 30.8, 49.2, 56.6, 125.6, 128.4, 169.3, 170.3, 172.9 ppm. HPLC [hexane/*i*PrOH (3:7) for 10 min, then in 5 min to 1:9, 1 mL/min]: t_R = 11.93 min [(*R*)-**15a**], t_R = 26.95 min [(*S*)-**15a**]. HRMS (CI): *m*/*z* calcd. $C_{46}H_{66}ClN_4O_9Si$ $[M + H]^+$ 881.4282; found 881.4313. $C_{46}H_{65}ClN_4O_9Si$ (881.57): calcd. C 62.67, H 7.43, N 6.36; found C 62.51, H 6.80, N 6.69.

***N*-*tert*-Butoxycarbonyl-(*S*)-alanyl-*N*-methyl-(*R*)-tryptophanyl-(*R*)-3-bromo-4-(*tert*-butyldimethylsilyloxy)-β-phenylalanine-{allyl [(*E*)-4-methylhept-4-enoate]-7-yl} Ester (15b):** Tripeptide **15b** was prepared according **14a** from β-tyrosine ester **13b** (0.25 g, 0.38 mmol), TFA (1.20 mL, 15.6 mmol) in abs. CH_2Cl_2 (2.7 mL) and dipeptide **4** (0.18 g, 0.46 mmol), *i*Pr_2NEt (0.12 mL, 0.69 mmol) and COMU® (0.20 g, 0.47 mmol) in abs. CH_2Cl_2 (2 mL). Purification by flash chromatography (petroleum ether/ethyl acetate, 7:3) provided **15b** (0.27 g, 0.29 mmol, 76%) as a pale yellow foam. R_f = 0.30 (petroleum ether/ethyl acetate, 1:1). 83:17 Mixture of diastereomers. Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.22 (s, 6 H), 0.94 (d, *J* = 6.8 Hz, 3 H), 1.03 (s, 9 H), 1.40 (s, 9 H), 1.61 (s,

3 H), 2.25 (td, *J* = 6.9, 6.9 Hz, 2 H), 2.31 (m, 2 H), 2.43 (m, 2 H), 2.76 (dd, *J* = 15.6, 7.0 Hz, 1 H), 2.85 (dd, *J* = 16.6, 8.8 Hz, 1 H), 2.92 (s, 3 H), 3.21 (dd, *J* = 15.7, 10.2 Hz, 1 H), 3.45 (dd, *J* = 15.8, 5.8 Hz, 1 H), 3.97 (t, *J* = 7.2 Hz, 2 H), 4.38 (dq, *J* = 6.8 Hz, 1 H), 4.56 (ddd, *J* = 5.8, 1.3, 1.3 Hz, 2 H), 5.09 (t, *J* = 7.0 Hz, 1 H), 5.20–5.36 (m, 4 H), 5.60 (dd, *J* = 9.9, 5.7 Hz, 1 H), 5.90 (ddt, *J* = 17.1, 10.3, 5.8 Hz, 1 H), 6.75 (d, *J* = 8.5 Hz, 1 H), 6.96–7.12 (m, 4 H), 7.16 (dd, *J* = 8.0, 8.0 Hz, 1 H), 7.32 (d, *J* = 8.0 Hz, 1 H), 7.38 (d, *J* = 1.8 Hz, 1 H), 7.59 (d, *J* = 8.0 Hz, 1 H), 8.16 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.3, 16.0, 17.0, 18.3, 23.2, 25.7, 27.3, 28.3, 30.8, 32.9, 34.5, 40.3, 46.6, 49.0, 56.7, 64.1, 65.1, 79.8, 111.0, 111.1, 115.3, 118.2, 118.5, 119.4, 119.8, 120.0, 122.0*, 122.1*, 126.4, 127.4, 131.2, 132.2, 134.9, 136.1, 136.6, 151.9, 155.6, 169.3, 170.4, 172.9, 174.3 ppm. (* *determined from CH-COSY*). Minor diastereomer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (s, 9 H), 1.44 (s, 9 H), 1.60 (s, 3 H), 3.14 (m, 1 H), 3.40 (m, 1 H), 3.91 (t, *J* = 7.3 Hz, 2 H), 6.80 (d, *J* = 8.3 Hz, 1 H), 8.22 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.4, 49.1, 136.5, 172.9 ppm. HPLC [hexane/*i*PrOH (3:7) for 10 min, then in 5 min to 1:9, 1 mL/min]: t_R = 12.88 min [(*R*)-**15b**], t_R = 30.25 min [(*S*)-**15b**]. HRMS (CI): *m*/*z* calcd. $C_{46}H_{66}BrN_4O_9Si$ [M + H]$^+$ 925.3777; found 925.3817.

***N*-*tert*-Butoxycarbonyl-(*S*)-alanyl-*N*-methyl-(*R*)-tryptophanyl-(*R*)-3-chloro-4-(*tert*-butyldimethylsilyloxy)-β-phenylalanine-{[(*E*)-4-methylhept-4-enoic acid]-7-yl} Ester (16a):** According to *N*,*O*-protected amino acid **8b**, **16a** was prepared from tripeptide **15a** (0.44 g, 0.50 mmol), $Pd(PPh_3)_4$ (57.0 mg, 0.05 mmol) and morpholine (0.09 mL, 0.99 mmol) in abs. THF (10 mL). Purification by flash chromatography [petroleum ether/ethyl acetate (6:4 to 1:1) + 1% AcOH] gave rise to **16a** (0.40 g, 0.48 mmol, 96%) as a pale yellow foam. R_f = 0.26 [petroleum ether/ethyl acetate (1:1) + 1% AcOH]. 73:27 Mixture of diastereomers. Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.21 (s, 6 H), 0.97 (d, *J* = 6.8 Hz, 3 H), 1.02 (s, 9 H), 1.41 (s, 9 H), 1.64 (s, 3 H), 2.21–2.39 (m, 4 H), 2.48 (m, 2 H), 2.67 (dd, *J* = 17.4, 6.2 Hz, 1 H), 2.84 (dd, *J* = 16.0, 9.3 Hz, 1 H), 2.99 (s, 3 H), 3.20 (dd, *J* = 15.3, 9.5 Hz, 1 H), 3.37 (dd, *J* = 14.8, 6.3 Hz, 1 H), 3.98 (m, 2 H), 4.48 (dq, *J* = 6.8, 6.8 Hz, 1 H), 5.19 (t, *J* = 7.0 Hz, 1 H), 5.31 (m, 1 H), 5.46–5.54 (m, 2 H), 6.77 (d, *J* = 8.5 Hz, 1 H), 6.92 (s, 1 H), 7.01 (dd, *J* = 8.5, 2.3 Hz, 1 H), 7.09 (dd, *J* = 7.9, 7.9 Hz, 1 H), 7.16 (dd, *J* = 7.5, 7.5 Hz, 1 H), 7.21 (d, *J* = 2.3 Hz, 1 H), 7.31 (d, *J* = 8.3 Hz, 1 H), 7.33 (br. s, 1 H), 7.57 (d, *J* = 7.8 Hz, 1 H), 8.09 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.4, 15.9, 17.5, 18.3, 23.4, 25.6, 27.2, 28.3, 30.9, 32.8, 34.7, 40.1, 46.8, 49.2, 56.7, 64.2, 79.8, 110.7, 111.1, 118.5, 119.4, 120.6, 120.6, 122.1, 122.3, 125.5, 125.7, 127.2, 128.2, 134.9, 136.1, 136.2, 150.8, 155.5, 169.4, 170.4, 174.3 ppm. Minor diastereomer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.20 (s, 6 H), 0.91 (d, *J* = 7.0 Hz, 3 H), 1.01 (s, 9 H), 1.43 (s, 9 H), 1.62 (s, 3 H), 2.80 (s, 3 H), 3.14 (m, 1 H), 3.42 (m, 1 H), 4.40 (m, 1 H), 5.14 (t, *J* = 6.5 Hz, 1 H), 5.59 (dd, *J* = 9.5, 6.3 Hz, 1 H), 6.82 (d, *J* = 8.5 Hz, 1 H), 8.16 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.2, 34.3, 39.9, 46.6, 121.0, 125.5, 125.6, 127.3, 128.4, 135.0, 170.2 ppm. HPLC/MS (H_2O/ACN, 3:7, 20 min, 0.6 mL/min): t_R = 13.65 min [(*R*)-**16a**], t_R = 14.40 min [(*S*)-**16a**], *m*/*z* calcd. $[C_{43}H_{61}ClN_4O_9Si + Na]^+$ 864; found 864. HRMS (CI): *m*/*z* calcd. $C_{43}H_{60}ClN_4O_9Si$ [M – H]$^-$ 839.3824; found 839.3816.

***N*-*tert*-Butoxycarbonyl-(*S*)-alanyl-*N*-methyl-(*R*)-tryptophanyl-(*R*)-3-bromo-4-(*tert*-butyldimethylsilyloxy)-β-phenylalanine-{[(*E*)-4-methylhept-4-enoic acid]-7-yl} Ester (16b):** According to *N*,*O*-protected amino acid **8b**, **16b** was prepared from tripeptide **15b** (0.25 g, 0.27 mmol), $Pd(PPh_3)_4$ (31.0 mg, 37.0 µmol) and morpholine (46.0 µL, 0.53 mmol) in abs. THF (5 mL). Purification by flash chromatography [petroleum ether/ethyl acetate (6:4 to 1:1) + 1% AcOH] gave rise to **16b** (0.23 g, 0.26 mmol, 96%) as a pale yellow foam. R_f = 0.29 [petroleum ether/ethyl acetate (1:1) + 1% AcOH]. 83:17 Mixture of diastereomers. Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.23 (s, 6 H), 0.95 (d, *J* = 7.5 Hz, 3 H), 1.02 (s, 9 H), 1.41 (s, 9 H), 1.64 (s, 3 H), 2.23 (m, 1 H), 2.28–2.38 (m, 3 H), 2.47 (m, 2 H), 2.67 (dd, *J* = 15.6, 4.5 Hz, 1 H), 2.84 (dd, *J* = 16.0, 9.3 Hz, 1 H), 2.99 (s, 3 H), 3.20 (dd, *J* = 15.6, 9.5 Hz, 1 H), 3.37 (dd, *J* = 15.2, 6.4 Hz, 1 H), 3.98 (m, 2 H), 4.47 (dq, *J* = 6.8, 6.8 Hz, 1 H), 5.19 (t, *J* = 7.0 Hz, 1 H), 5.29 (m, 1 H), 5.47–5.54 (m, 2 H), 6.76 (d, *J* = 8.3 Hz, 1 H), 6.92 (s, 1 H), 7.05 (dd, *J* = 8.5, 2.3 Hz, 1 H), 7.09 (dd, *J* = 7.8, 7.8 Hz, 1 H), 7.16 (dd, *J* = 7.5, 7.5 Hz, 1 H), 7.31 (d, *J* = 8.0 Hz, 1 H), 7.36 (br. s, 1 H), 7.39 (d, *J* = 8.0 Hz, 1 H), 7.57 (d, *J* = 7.8 Hz, 1 H), 8.13 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.4, 15.9, 17.5, 18.3, 23.4, 25.7, 27.2, 28.3, 30.9, 32.8, 34.7, 40.1, 46.7, 49.1, 56.7, 64.2, 79.8, 110.7, 111.1, 115.3, 118.5, 119.4, 120.0, 121.0, 122.0, 122.2, 126.5, 127.2, 131.2, 135.2, 136.0, 136.1, 151.8, 155.5, 169.4, 170.4, 174.3, 175.5 ppm. Minor diastereomer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.22 (s, 6 H), 0.90 (d, *J* = 8.0 Hz, 3 H), 1.02 (s, 9 H), 1.43 (s, 9 H), 1.62 (s, 3 H), 2.80 (s, 3 H), 3.13 (m, 1 H), 3.43 (m, 1 H), 4.41 (m, 1 H), 5.36 (m, 1 H), 5.60 (dd, *J* = 9.5, 6.0 Hz, 1 H), 6.80 (d, *J* = 8.3 Hz, 1 H), 6.98 (s, 1 H), 8.21 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.3, 49.3, 56.7, 120.1, 126.4, 175.6 ppm. HPLC/MS (H_2O/ACN, 3:7, 20 min, 0.6 mL/min): t_R = 14.58 min [(*R*)-**16b**], t_R = 15.15 min [(*S*)-**16b**], *m*/*z* calcd. $[C_{43}H_{61}BrN_4O_9Si + Na]^+$ 907; found 907. HRMS (CI): *m*/*z* calcd. $C_{43}H_{62}BrN_4O_9Si$ [M + H]$^+$ 885.3464; found 885.3495

***N*-*tert*-Butoxycarbonyl-(*S*)-alanyl-*N*-methyl-(*R*)-2-chlorotryptophanyl-(*R*)-3-chloro-4-(*tert*-butyldimethylsilyloxy)-β-phenylalanine-{[(*E*)-4-methylhept-4-enoic acid]-7-yl} Ester (16c):** According to *N*,*O*-protected amino acid **8b**, **16c** was prepared from tripeptide **14a** (0.32 g, 0.35 mmol), $Pd(PPh_3)_4$ (40.0 mg, 35.0 µmol) and morpholine (61 µL, 0.70 mmol) in abs. THF (3.5 mL). Purification by flash chromatography [petroleum ether/ethyl acetate (7:3 to 1:1) + 1% AcOH] gave rise to **16c** (0.30 g, 0.34 mmol, 97%) as a colorless foam. R_f = 0.14 [petroleum ether/ethyl acetate (7:3) + 1% AcOH]. $[\alpha]_D^{20}$ = +7.4 (*c* = 1.5, $CHCl_3$). 91:9 Mixture of diastereomers. Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.22 (s, 6 H), 0.70 (d, *J* = 6.8 Hz, 3 H), 1.02 (s, 9 H), 1.38 (s, 9 H), 1.64 (s, 3 H), 2.21 (m, 1 H), 2.28–2.41 (m, 3 H), 2.48 (m, 2 H), 2.68 (dd, *J* = 15.8, 5.5 Hz, 1 H), 2.85 (dd, *J* = 16.0, 9.3 Hz, 1 H), 3.01 (s, 3 H), 3.22 (dd, *J* = 15.1, 10.0 Hz, 1 H), 3.30 (dd, *J* = 15.6, 6.5 Hz, 1 H), 3.98 (m, 2 H), 4.37 (dq, *J* = 7.0, 7.0 Hz, 1 H), 5.18 (t, *J* = 7.0 Hz, 1 H), 5.27–5.32 (m, 2 H), 5.63 (dd, *J* = 9.8, 6.0 Hz, 1 H), 6.77 (d, *J* = 8.3 Hz, 1 H), 7.03 (dd, *J* = 9.0, 2.5 Hz, 1 H), 7.07 (dd, *J* = 8.0, 8.0 Hz, 1 H), 7.12 (dd, *J* = 7.8, 7.8 Hz, 1 H), 7.19–7.23 (m, 2 H), 7.31 (d, *J* = 7.0 Hz, 1 H), 7.47 (d, *J* = 7.8 Hz, 1 H), 8.06 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.3, 15.9, 17.6, 18.3, 22.5, 25.6, 27.2, 28.3, 31.3, 32.8, 34.7, 40.2, 46.6, 49.3, 55.7, 64.2, 79.8, 107.0, 110.4, 118.3, 120.2, 120.6, 120.9, 121.7, 122.4, 125.5, 125.8, 127.3, 128.2, 134.3, 134.8, 136.1, 150.8, 155.5, 169.3, 170.3, 174.2, 175.5 ppm. Minor diastereomer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41 (s, 9 H), 1.66 (s, 3 H), 2.21 (m, 1 H), 2.72 (s, 3 H), 2.77 (m, 1 H), 2.77 (m, 1 H), 4.06 (m, 2 H), 4.52 (m, 1 H), 5.02 (m, 1 H), 5.46 (m, 1 H) ppm. HPLC/MS (H_2O/ACN, 2:8, 20 min, 0.6 mL/min): t_R = 2.78 min [(*R*/*S*)-**16c**], *m*/*z* calcd. $[C_{43}H_{60}Cl_2N_4O_9Si + Na]^+$ 897; found 897. HRMS (CI): *m*/*z* calcd. $C_{43}H_{61}Cl_2N_4O_9Si$ [M + H]$^+$ 875.3579; found 875.3621.

(4*R*,7*R*,10*S*,*E*)-7-(1*H*-indol-3-ylmethyl)-4-(4-*tert*-butyldimethylsilyloxy-3-chlorophenyl)-8,10,15-trimethyl-1-oxa-5,8,11-triazacyclooctadec-15-ene-2,6,9,12-tetraone (17a): To a solution of tripeptide **16a** (0.25 g, 0.30 mmol) in abs. CH_2Cl_2 (2.6 mL) TFA (1.16 mL, 15.1 mmol) was added at –20 °C and the mixture was stirred for

16 h at this temperature. The solvent was removed under reduced pressure and the crude amine was redissolved in abs. CH_2Cl_2 (150 mL). iPr$_2$NEt (0.21 mL, 1.19 mmol) and T3P® (0.65 g, 1.04 mmol, 50 wt.-% in ethyl acetate) were added at 0 °C. The reaction mixture was warmed to room temperature overnight, concentrated to dryness and the residue was dissolved in ethyl acetate. The organic layer was washed with HCl (1 M), satd. $NaHCO_3$, H_2O, brine, dried with Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (ethyl acetate) resulted in the isolation of **17a** (93.0 mg, 0.13 mmol, 43%) as a colorless solid M.p. 98–100 °C. R_f = 0.20 (ethyl acetate). $[\alpha]_D^{20}$ = +20.5 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.21 (s, 6 H), 0.97 (d, J = 6.8 Hz, 3 H), 1.02 (s, 9 H), 1.64 (s, 3 H), 2.20 (m, 2 H), 2.31–2.39 (m, 4 H), 2.68 (dd, J = 16.6, 3.5 Hz, 1 H), 2.81 (dd, J = 16.5, 10.0 Hz, 1 H), 2.94 (s, 3 H), 3.21 (dd, J = 15.8, 10.0 Hz, 1 H), 3.36 (dd, J = 15.6, 5.3 Hz, 1 H), 3.99 (m, 2 H), 4.54 (dq, J = 6.8 Hz, 1 H), 5.09 (t, J = 7.2 Hz, 1 H), 5.25 (ddd, J = 10.0, 7.8, 3.3 Hz, 1 H), 5.55 (dd, J = 10.0, 6.3 Hz, 1 H), 6.38 (d, J = 5.5 Hz, 1 H), 6.79 (d, J = 8.3 Hz, 1 H), 6.94 (d, J = 2.3 Hz, 1 H), 6.98 (dd, J = 8.3, 2.3 Hz, 1 H), 7.08–7.12 (m, 2 H), 7.17 (dd, J = 7.0 Hz, 1 H), 7.19 (d, J = 2.3 Hz, 1 H), 7.32 (d, J = 8.0 Hz, 1 H), 7.59 (d, J = 7.8 Hz, 1 H), 8.07 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.4, 16.1, 17.3, 18.3, 23.2, 25.6, 27.1, 30.7, 34.5, 35.6, 40.2, 46.0, 48.9, 56.3, 64.8, 110.9, 111.1, 118.5, 119.4, 120.6, 121.4, 122.1, 122.1, 125.4, 125.6, 127.3, 127.8, 135.1, 135.8, 136.1, 150.7, 169.5, 170.6, 171.8, 174.1 ppm. HPLC/MS (H_2O/ACN, 3:7, 20 min, 0.6 mL/min): t_R = 11.73 min, m/z calcd. $[C_{38}H_{51}ClN_4O_6Si + Na]^+$ 745; found 745. HRMS (CI): m/z calcd. $C_{38}H_{52}ClN_4O_6Si$ $[M + H]^+$ 723.3339; found 723.3324.

(4*R*,7*R*,10*S*,*E*)-7-(1*H*-indol-3-ylmethyl)-4-(3-bromo-4-*tert*-butyldimethylsilyloxyphenyl)-8,10,15-trimethyl-1-oxa-5,8,11-triazacyclooctadec-15-ene-2,6,9,12-tetraone (17b): Macrocycle **17b** was prepared according to **17a** from tripeptide **16b** (205 mg, 231 μmol), TFA (0.89 mL, 11.6 mmol) in abs. CH_2Cl_2 (2 mL) and iPr$_2$NEt (0.16 mL, 0.93 mmol), T3P®[26] (0.51 g, 0.81 mmol, 50 wt.-% in ethyl acetate) in abs. CH_2Cl_2 (120 mL). Purification by flash chromatography (ethyl acetate) provided **17b** (93.0 mg, 121 μmol, 52%) as a colorless solid, m.p. 88–90 °C. R_f = 0.21 (ethyl acetate). $[\alpha]_D^{20}$ = +17.6 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.23 (s, 6 H), 0.97 (d, J = 7.0 Hz, 3 H), 1.03 (s, 9 H), 1.64 (s, 3 H), 2.20 (m, 2 H), 2.31–2.39 (m, 4 H), 2.67 (dd, J = 16.6, 3.3 Hz, 1 H), 2.79 (dd, J = 16.8, 10.3 Hz, 1 H), 2.93 (s, 3 H), 3.21 (dd, J = 15.8, 10.0 Hz, 1 H), 3.37 (dd, J = 15.3, 5.8 Hz, 1 H), 3.99 (m, 2 H), 4.52 (dq, J = 6.5, 6.5 Hz, 1 H), 5.09 (t, J = 7.2 Hz, 1 H), 5.25 (ddd, J = 10.5, 7.8, 3.3 Hz, 1 H), 5.56 (dd, J = 9.9, 6.2 Hz, 1 H), 6.37 (d, J = 5.8 Hz, 1 H), 6.77 (d, J = 8.3 Hz, 1 H), 6.95 (d, J = 2.0 Hz, 1 H), 7.03 (dd, J = 8.4, 2.1 Hz, 1 H), 7.08–7.13 (m, 2 H), 7.17 (dd, J = 7.0, 7.0 Hz, 1 H), 7.32 (d, J = 7.8 Hz, 1 H), 7.38 (d, J = 2.0 Hz, 1 H), 7.59 (d, J = 7.8 Hz, 1 H), 8.13 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.2, 16.1, 17.3, 18.3, 23.1, 25.7, 27.1, 30.6, 34.5, 35.7, 40.2, 46.0, 48.8, 56.2, 64.8, 110.9, 111.1, 115.4, 118.5, 119.4, 119.9, 121.4, 122.0, 122.1, 126.2, 127.3, 130.9, 135.4, 135.8, 136.1, 151.8, 169.5, 170.6, 171.7, 174.0 ppm. HPLC/MS (H_2O/ACN, 3:7, 20 min, 0.6 mL/min): t_R = 11.73 min, m/z calcd. $[C_{38}H_{51}BrN_4O_6Si + Na]^+$ 789; found 789. HRMS (CI): m/z calcd. $C_{38}H_{51}BrN_4O_6Si$ $[M]^+$ 766.2756; found 726.2741.

(4*R*,7*R*,10*S*,*E*)-7-(1*H*-Indol-3-ylmethyl)-4-(3-chloro-4-hydroxyphenyl)-8,10,15-trimethyl-1-oxa-5,8,11-triazacyclooctadec-15-ene-2,6,9,12-tetraone (18a): To a solution of **17a** (68.0 mg, 94.0 μmol) in abs. THF (1 mL) TBAF (27.0 mg, 0.10 mmol) was added. The mixture was stirred overnight at room temperature, diluted with ethyl acetate and washed with HCl (1 M) and brine and dried with Na_2SO_4. Removal of the solvent under reduced pressure and purification by flash chromatography (ethyl acetate) resulted in the isolation of **18a** (47.0 mg, 77.0 μmol, 82%) as a colorless solid, m.p. 122–126 °C. R_f = 0.16 (ethyl acetate). $[\alpha]_D^{20}$ = +4.0 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (d, J = 5.0 Hz, 3 H), 1.63 (s, 3 H), 1.71 (br. s, 1 H, OH), 2.17–2.42 (m, 6 H), 2.64 (d, J = 16.0 Hz, 1 H), 2.86 (dd, J = 16.9, 11.2 Hz, 1 H), 2.94 (s, 3 H), 3.20 (dd, J = 15.8, 10.3 Hz, 1 H), 3.42 (dd, J = 15.8, 5.8 Hz, 1 H), 3.93 (m, 1 H), 4.05 (ddd, J = 10.8, 10.8, 2.8 Hz, 1 H), 4.54 (m, 1 H), 5.08 (t, J = 7.2 Hz, 1 H), 5.19 (m, 1 H), 5.63 (dd, J = 9.3, 5.3 Hz, 1 H), 6.27 (br. s, 1 H), 6.83 (m, 1 H), 6.92–6.96 (m, 2 H), 7.09 (d, J = 7.3 Hz, 1 H), 7.15 (dd, J = 7.5 Hz, 1 H), 7.20 (d, J = 2.0 Hz, 1 H), 7.31 (d, J = 8.0 Hz, 1 H), 7.35 (br. s, 1 H), 7.58 (d, J = 8.0 Hz, 1 H), 8.17 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.0, 16.7, 23.0, 27.1, 30.8, 34.4, 36.2, 40.3, 46.0, 49.3, 56.5, 64.7, 110.9, 111.1, 116.6, 118.5, 119.4, 120.1, 121.4, 122.0, 122.0, 125.6, 127.2, 127.4, 135.5, 136.1, 136.1, 151.1, 169.6, 170.6, 172.2, 174.2 ppm. HRMS (CI): m/z calcd. $C_{32}H_{38}ClN_4O_6$ $[M + H]^+$ 609.2474; found 609.2503.

(4*R*,7*R*,10*S*,*E*)-7-(1*H*-Indol-3-ylmethyl)-4-(3-bromo-4-hydroxyphenyl)-8,10,15-trimethyl-1-oxa-5,8,11-triazacyclooctadec-15-ene-2,6,9,12-tetraone (18b): According to macrocycle **18a**, **18b** was prepared from **17b** (73.0 mg, 95.0 μmol) and TBAF (36.0 mg, 0.11 mmol) in abs. THF (1 mL). Purification by flash chromatography (ethyl acetate) gave rise to **18b** (39.0 mg, 60.0 μmol, 63%) as a colorless solid, m.p. 129–132 °C. R_f = 0.18 (ethyl acetate). $[\alpha]_D^{20}$ = +7.8 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (d, J = 7.0 Hz, 3 H), 1.62 (s, 3 H), 2.10–2.31 (m, 5 H), 2.41 (m, 1 H), 2.62 (dd, J = 16.9, 2.9 Hz, 1 H), 2.88 (dd, J = 17.1, 11.0 Hz, 1 H), 2.93 (s, 3 H), 3.17 (dd, J = 15.9, 10.4 Hz, 1 H), 3.43 (dd, J = 15.9, 5.7 Hz, 1 H), 3.91 (m, 1 H), 4.05 (ddd, J = 10.5, 2.3 Hz, 1 H), 4.38 (dq, J = 6.8 Hz, 1 H), 5.06 (t, J = 7.3 Hz, 1 H), 5.17 (ddd, J = 10.3, 6.8, 3.0 Hz, 1 H), 5.66 (dd, J = 10.3, 5.8 Hz, 1 H), 6.33 (d, J = 4.8 Hz, 1 H), 6.78 (d, J = 8.5 Hz, 1 H), 6.89 (d, J = 1.8 Hz, 1 H), 6.93 (dd, J = 8.5, 2.0 Hz, 1 H), 7.07 (dd, J = 7.4 Hz, 1 H), 7.13 (dd, J = 7.2 Hz, 1 H), 7.29 (d, J = 8.0 Hz, 1 H), 7.36 (d, J = 2.0 Hz, 1 H), 7.46 (d, J = 6.8 Hz, 1 H), 7.56 (d, J = 7.8 Hz, 1 H), 7.87 (br. s, 1 H), 8.31 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.9, 16.4, 22.9, 27.0, 30.9, 34.3, 36.4, 40.3, 46.0, 49.4, 56.5, 64.6, 110.0, 110.8, 111.1, 116.4, 118.4, 119.2, 121.4, 121.9, 122.0, 126.1, 127.4, 130.4, 134.8, 136.1, 136.2, 152.3, 169.7, 170.7, 172.4, 174.4 ppm. HRMS (CI): m/z calcd. $C_{32}H_{38}BrN_4O_6$ $[M + H]^+$ 653.1969; found 653.1951.

(4*R*,7*R*,10*S*,*E*)-7-(2-Chloro-1*H*-indol-3-ylmethyl)-4-(3-chloro-4-hydroxyphenyl)-8,10,15-trimethyl-1-oxa-5,8,11-triazacyclooctadec-15-ene-2,6,9,12-tetraone (18c): According to the cyclization and deprotection procedure of **17a** and **18a**, **18c** was prepared from **16c** (0.28 g, 0.32 mmol), TFA (0.98 mL, 12.7 mmol) in abs. CH_2Cl_2 (2.3 mL), and iPr$_2$NEt (0.28 mL, 1.59 mmol), T3P® (0.80 g, 1.27 mmol, 50 wt.-% in ethyl acetate) in abs. CH_2Cl_2 (80 mL) and TBAF (0.35 mL, 0.35 mmol, 1 M in THF) in abs. THF (2.3 mL). Purification by flash chromatography (petroleum ether/ethyl acetate, 2:8) and by Prep-HPLC (ACN/H_2O) provided **18c** (113 mg, 176 μmol, 55%) as a colorless solid, m.p. 147–150 °C. R_f = 0.17 (petroleum ether/ethyl acetate, 2:8). $[\alpha]_D^{20}$ = +27.7 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.70 (d, J = 6.8 Hz, 3 H), 1.61 (s, 3 H), 2.10–2.31 (m, 5 H), 2.39 (m, 1 H), 2.63 (d, J = 17.1, 3.0 Hz, 1 H), 2.87 (dd, J = 17.7, 11.0 Hz, 1 H), 2.98 (s, 3 H), 3.19 (dd, J = 15.3, 10.8 Hz, 1 H), 3.35 (dd, J = 15.3, 5.3 Hz, 1 H), 3.93 (m, 1 H), 4.04 (ddd, J = 10.5, 10.5, 2.5 Hz, 1 H), 4.31 (dq, J = 6.8 Hz, 1 H), 5.05 (t, J = 7.3 Hz, 1 H), 5.18 (ddd, J = 10.0, 6.5, 2.8 Hz, 1 H), 5.65 (dd, J = 10.9, 5.4 Hz, 1 H), 6.17 (d, J = 4.8 Hz, 1 H), 6.81 (d, J = 8.3 Hz, 1 H), 6.97 (dd, J = 8.3, 2.0 Hz, 1 H), 7.05 (ddd, J = 8.0, 8.0, 1.0 Hz, 1 H), 7.11 (ddd, J = 7.3, 7.3, 1.3 Hz, 1 H), 7.18

(d, J = 8.0 Hz, 1 H), 7.21 (d, J = 2.3 Hz, 1 H), 7.33 (d, J = 6.8 Hz, 1 H), 7.46 (d, J = 7.8 Hz, 1 H), 8.47 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.9, 16.2, 21.9, 27.0, 31.4, 34.4, 36.4, 40.3, 45.8, 49.5, 56.0, 64.7, 107.2, 110.5, 116.6, 118.1, 120.1, 120.1, 121.4, 121.6, 122.2, 125.7, 127.2, 127.3, 134.4, 134.5, 136.1, 151.1, 169.6, 170.7, 172.2, 174.2 ppm. HPLC/MS (H_2O/ACN, 1:1, 10 min, 0.6 mL/min): t_R = 2.05 min *m/z* calcd. $[C_{32}H_{36}Cl_2N_4O_6 + Na]^+$ 665; found 665. HRMS (CI): *m/z* calcd. $C_{32}H_{37}Cl_2N_4O_6$ $[M + H]^+$ 643.2085; found 643.2098.

Supporting Information (see footnote on the first page of this article): Copies of NMR spectra as well as HPLC and LC-MS data of all new compounds.

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