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Backbone Amide Linker Strategy for the Synthesis of 1,4-Triazole-Containing Cyclic Tetra- and Pentapeptides

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A backbone amide linker strategy was chosen for the solid-phase synthesis of triazole-containing cyclic tetra- and pentapeptides. An alkyne-substituted linker derived from 4-hydroxy-2-methoxybenzaldehyde was elongated by using standard "Fmoc-based" solid phase chemistry and terminated by coupling of an azido acid. In solution, the peptides were cyclized by a Cu^{I}-catalyzed azide-alkyne cycloaddition reaction. The solid-supported synthesized linear peptides had to be cleaved prior to cyclization. As an example of cyclic tetrapeptides, a triazole analog of *cyclo*-[Pro-Val-Pro-Tyr] (**2**) was prepared by the solid-phase/solution-phase method. For the cyclic pentapeptides, segetalin B (**3**) was chosen as a model compound to show the applicability of this method.

Introduction

Small cyclic peptides comprise a priviliged class of compounds,[1] and many – such as gramicidin S,[2] tentoxin[3] and apicidin[4] – show relevant biological activities. A library of analogs of these compounds would be a valuable tool not only for the identification of the pharmacophoric properties on existing targets, but also on new biological targets and to carefully investigate the interactions with these proteins. Because of the vast array of available natural and unnatural amino acids carrying diverse functional groups, cyclic peptide properties can be easily varied.

The synthesis of small cyclic peptides may be hampered by the cyclization step.[5] Small peptide lactamization is often low-yielding and leads to the formation of unwanted oligomers and polymers. These difficulties are due to the nature of the amide bonds of the linear peptide, which preferentially adopt a *transoid* character. This places the mutually reactive C- and N-termini of the linear peptide far apart,[6] providing difficulties in the final lactamization reaction.

It has been shown earlier that the Cu^{I}-catalyzed 1,3-dipolar cycloaddition reaction between an alkyne and an azide to give a 1,4-connected 1,2,3-triazole moiety provides a powerful tool for the cyclization of such peptides.[7] We have shown recently that the natural tyrosinase inhibitor all-L cyclic tetrapeptide *cyclo*-[Pro-Val-Pro-Tyr][8] (**1**, Figure 1), which could not be prepared by traditional lactamization strategies, could be ring-closed easily as a triazole-containing analog.[9] Substitution of the C-terminus by an alkyne and the N-terminus by an azide gave the linear precursor for the 1,3-dipolar cycloaddition reaction, that was carried out subsequently to give the cyclic pseudopeptide in an excellent 70% yield.[9a] Moreover, the tyrosinase inhibitory activity was retained,[9b] showing that the triazole acts in this case as a mimic for the replaced amide bond. These findings are in line with results reported by Ghadiri et al. who have shown the similarity between a 1,4-connected tri-

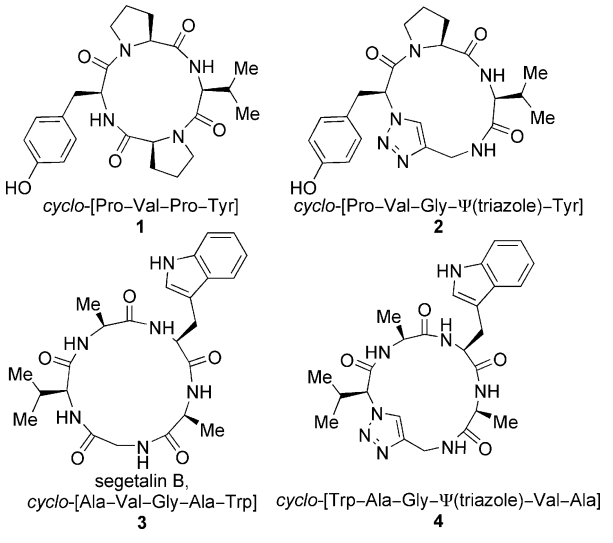

Figure 1. Cyclic peptides **1** and **3** and their triazole analogs **2** and **4**.

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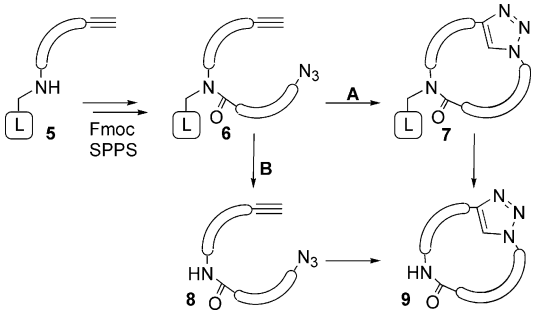
azole and a *trans* amide bond in peptides in terms of electronic, steric and hydrogen-bond-donating and -accepting capacities.[10]

This paper describes an extension of our work to enable parallel access to triazole-containing cyclic pseudopeptides. Since the introduction of solid-phase peptide synthesis (SPPS) by Merrifield in 1963,[11] this field has emerged and has led to several strategies for the combinatorial synthesis of cyclic peptides.[12] For the solid-phase synthesis of triazole-containing cyclic pseudopeptides we selected a so-called backbone amide linker (BAL) for anchoring of the linear cyclization precursors, thereby introducing a tertiary amide bond inducing a turn in the peptide chain facilitating cyclization.[13,14] The use of an acid-labile backbone amide linker (**5**, Scheme 1) in combination with Fmoc-SPPS ensures a facile synthesis of the linear peptide precursors **6** after which the cyclization can be performed on the solid support (route A) or in solution after cleavage (route B).

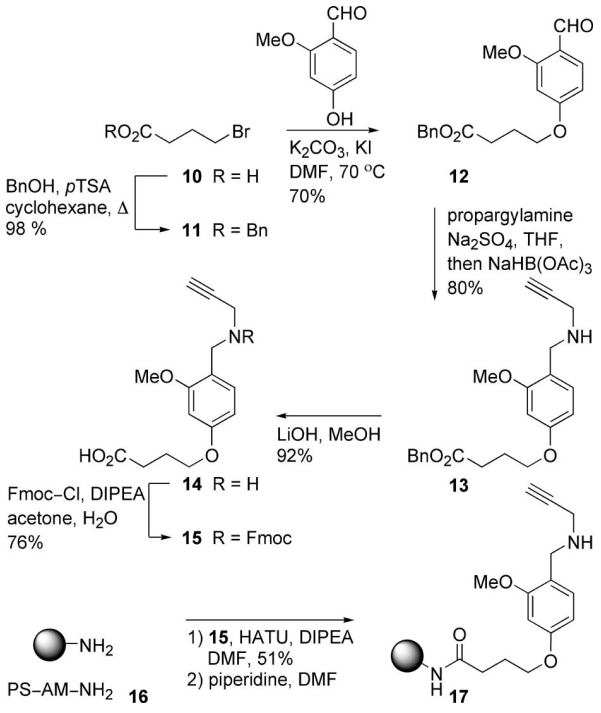


Scheme 1. Strategy for the combinatorial synthesis of triazole-containing cyclic peptides **9**.

Two model cyclic peptides were selected to develop the new chemistry, i.e. *cyclo*-[Pro-Val-Gly-ψ(triazole)-Tyr] (**2**), derived from the naturally occurring cyclic tetrapeptide **1** which was isolated from *L. helveticus* and shows tyrosinase inhibition activity,[9] and *cyclo*-[Trp-Ala-Gly-ψ(triazole)-Val-Ala] (**4**) which is the triazole analog of the cyclic pentapeptide segetalin B (**3**), isolated from the seeds of *Vaccaria segetalis* (Figure 1).[15] The site for the introduction of the ψ(triazole) moiety in **2** and **4** was selected by the presence of a *trans* amide bond configuration at these positions in the natural congeners.

Results and Discussion

The benzyl 4-(4-formyl-3-methoxyphenoxy)butanoate linker (**12**, Scheme 2) which was chosen is based on anchoring of a backbone amide bond by an acid-labile benzylic bond. The synthesis of the cyclic pseudopeptides with the linker system was first validated in solution from the benzyl ester **13**. The aldehyde linker could be prepared in two steps from commercially available starting materials (Scheme 2). Protection of the acid moiety of 4-bromobutanoic acid (**10**) yielded the benzyl ester **11** in 98% yield.[16] Alkylation of 4-hydroxy-2-methoxybenzaldehyde with the bromide **11** provided **12** in 70% yield. The linker **12** was loaded with propargylamine by a reductive amination to afford **13**. To allow attachment of **13** onto the solid support, the benzyl ester was saponified with lithium hydroxide in MeOH. Subsequent protection of the amine with Fmoc chloride and DIPEA furnished **15** in 76% yield which was loaded on polystyrene resin functionalized with primary amine (PS-AM-NH_2, **16**) by coupling using HATU/DIPEA in DMF in 51% yield, as determined by the Fmoc-loading test.[17] Treatment of the resin with piperidine liberated the propargylic amine **17** ready for acylation.



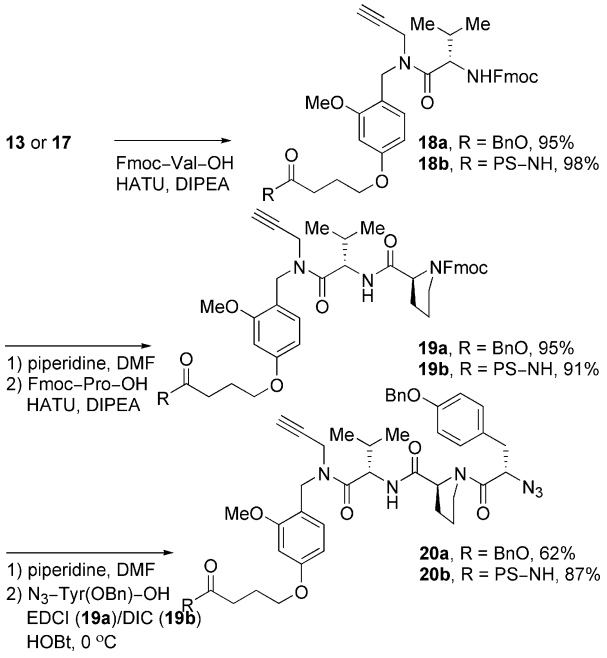
Scheme 2. Synthesis of the solution-phase linker **13** and the solid-phase linker **17**.

The synthesis of the solution-phase linear precursor **20a** started from **13** by coupling of Fmoc-Val-OH using HATU as the coupling reagent to give **18a** in 95% yield (Scheme 3).

Fmoc removal of **18a** with piperidine followed by coupling with Fmoc-Pro-OH using similar conditions provided the pseudo-tripeptide **19a** in 95% overall yield. To suppress epimerization, the final azido acid N_3-Tyr(OBn)-OH[18] was coupled using EDCI/HOBt at 0 °C to give the desired linear tetrapeptide precursor **20a** in 62% yield.

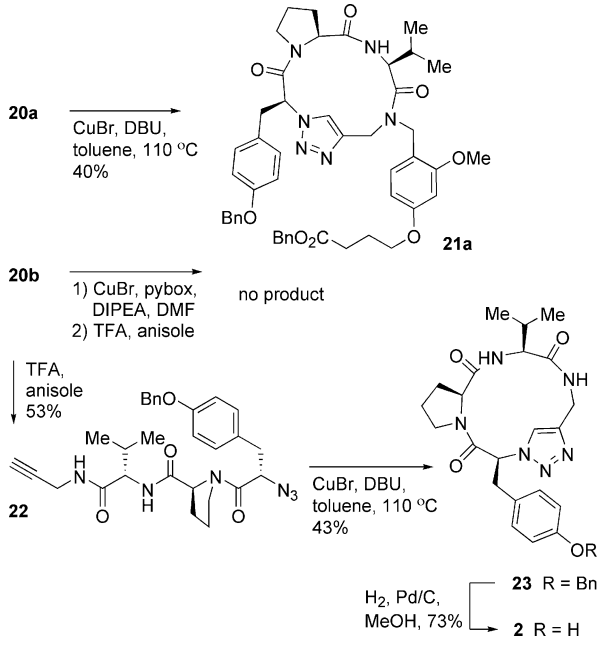
The solid-phase synthesis of the linear precursor **20b** started by coupling of Fmoc-Val-OH to the resin **17** using similar reagents as mentioned above in excess, to afford the product in 98% yield (Scheme 3). Fmoc removal and coupling of Fmoc-Pro-OH afforded the tripeptide **19b**. Final coupling of N_3-Tyr(OBn)-OH using DIC and HOBt at 0 °C afforded the cyclization precursor **20b** in 87% yield.

Now the stage was set for the Cu^I-catalyzed cyclization reaction. Although several conditions for the macrocyclization were evaluated, the conditions of choice were similar as described previously (Scheme 4). Thus, treatment of **20a** in solution with CuBr and an excess of DBU in refluxing toluene afforded the cyclic peptide **21a** in 40% isolated yield. However, subjection of the immobilized linear precur-



Scheme 3. Synthesis of the linear precursors in solution **20a** from **13** and on the solid phase **20b** from **17**.

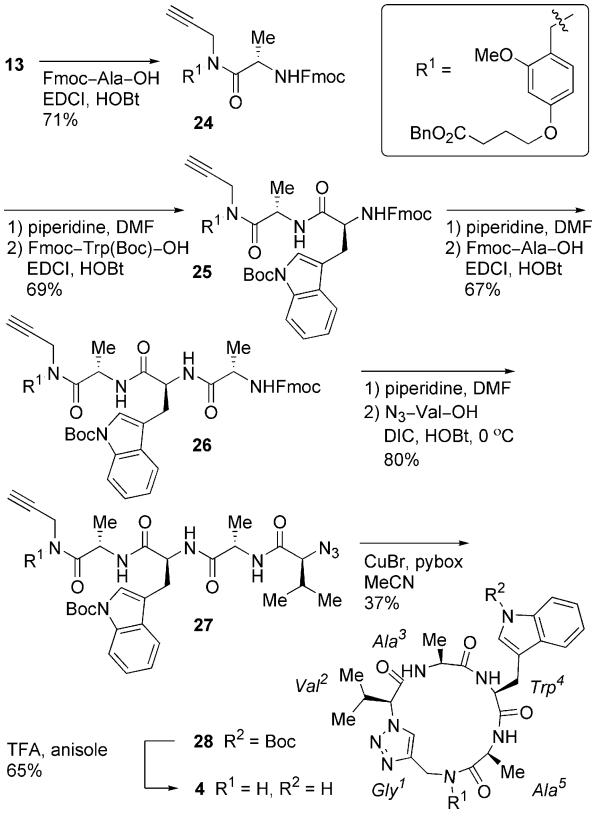
sor **20b** to the cycloaddition conditions and subsequent cleavage of the cyclic peptide from the resin with TFA (cf. route A, Scheme 1) only afforded unidentified side products. IR spectroscopy revealed complete disappearance of the azide signal on the resin.



Scheme 4. Cyclization of the linear precursors **20a** and **20b** to afford the cyclic peptides **21a** and **2**, respectively.

As an alternative, the immobilized cyclization precursor **20b** was cleaved off by treatment with TFA to liberate the linear precursor **22** (53% crude overall yield) to which CuBr and DBU in refluxing toluene were added (cf. route B, Scheme 1) to afford cyclic peptide **23** in 43% isolated yield. Final hydrogenolytic removal of the tyrosine benzylic ether protective group furnished the target peptide *cyclo*-[Pro-Tyr-ψ(triazole)-Gly-Val] **2** in 73% yield.

To show the applicability of our method in the cyclic pentapeptide series, the triazole analog **4** of segetalin B {*cyclo*-[Ala-Val-Gly-Ala-Trp] (**3**)} was chosen (Scheme 5) as a model pentapeptide. Starting from the solution-phase linker **13**, the proper Fmoc-protected amino acids were coupled in good yields (67–71%) using EDCI/HOBt, and finally N_3-Val-OH was attached to furnish the linear pentapeptide **27** in 80% yield. Cyclization was performed using CuBr and a pybox-type ligand in acetonitrile at room temperature[19] to afford the cyclic peptide **28** in 37% yield along with 10% of the dimer, which could be easily separated by flash column chromatography. Final removal of the linker and the protective group of the tryptophan residue afforded the triazole analog **4** of segetalin B in 65% isolated yield.



Scheme 5. Synthesis of the triazole analog **4** of segetalin B in solution from **13**.

To investigate the influence of substitution of an amide group for a 1,4-connected triazole moiety on the conformation of the cyclic pentapeptide, NMR studies were performed. All proton and carbon signals could be assigned by COSY, HMBC and HMQC NMR experiments. Both proton and carbon NMR spectra indicated the presence of only one stable conformer in solution, as only sharp and single peaks were observed.

To determine whether intramolecular hydrogen bonds are present, the temperature dependence of the amide proton chemical shifts was examined by NMR spectroscopy.[20] The chemical shifts of the amide N*H* protons in [D_6]DMSO were monitored during elevation of the temperature from 300 to 330 K. The temperature coefficients which were obtained are shown in Table 1.

Table 1. Temperature coefficients ($-d\delta/dT \times 10^{-3}$ ppm/K) of the amide protons in cyclic peptide **4**.

Solvent	Gly[1]	Ala[3]	Trp[4]	Ala[5]
[D_6]DMSO	6.4	7.0	0.8	8.9

On raising the temperature, all intermolecular hydrogen bonds will be broken, while intramolecular hydrogen bonds remain intact. When the temperature coefficient for the N*H* signals is larger than 4×10^{-3} ppm/K (in [D_6]DMSO), it is considered to indicate external N*H* orientation. In the case of intramolecular hydrogen bonds using DMSO as the solvent, values will be lower then 2×10^{-3} ppm/K. As can be seen in Table 1, only the amide-N*H* of Trp seems to be involved in intramolecular hydrogen bonding, in contrast to the parent natural cyclic peptide segetalin B where none of the amide N*H* bonds are involved in intramolecular hydrogen bonding.

Comparison of 2D NOE spectra of the cyclic peptide analog **4** with NOE correlations found for segetalin B, could provide information whether the conformation was retained upon introduction of the triazole linkage (Figure 2). The most important NOE correlations of segetalin B and the triazole analog **4** are shown. Segetalin B is thought to adopt a type-II β-turn in the Ala-Trp-Ala-Gly region of the natural peptide, as can be seen by specific NOE enhancements of $C_\alpha H$ of the Trp, the $C_\alpha H$ of the Ala and the N*H* of the Ala residue.[21] In the region which is expected to have a type-II β-turn conformation, the NOE correlations found for the cyclic peptide analog **4**, correspond to the NOE correlations given for the natural product segetalin B (Figure 2).[15a] NOESY spectra show correlations between the Ala[5] $C_\alpha H$ and the Ala[5] N*H*. Also the correlation between the Ala[5] N*H* with the Trp $C_\alpha H$ is seen. These NOE enhancements are also found in the natural product and suggest that the triazole-containing analog adopts the same type-II β-turn as the natural product.

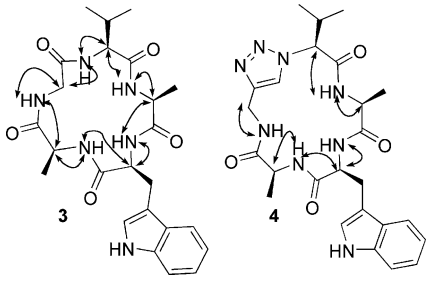


Figure 2. NOE correlations of cyclic peptide segetalin B (**3**) and its analog **4**.

The NOE correlation spectra also provide information about whether the amide bonds are *cisoid* or *transoid*. In the case of *cisoid* amide bonds, NOE correlations between adjacent $C_\alpha H$ can be expected. As no $C_\alpha H$-$C_\alpha H$ correlations were observed, it is likely that in the triazole analog **4** all amide bonds are in the *transoid* form. Further ongoing conformational studies in combination with molecular modeling and biological testing should provide more refined conclusions on the exact conformation of the triazole analog.

Conclusions

This research has shown the syntheses of the triazole-containing analog of cyclic tetrapeptide *cyclo*-[Pro-Val-Gly-ψ(triazole)-Tyr] (**2**) by means of a backbone amide linkage strategy in solution and on a solid phase. It was found that cleavage of the linear precursor from the resin was necessary prior to cyclization by an azide/alkyne 1,3-dipolar cycloaddition in solution. The triazole analog of the cyclic pentapeptide segetalin B, *cyclo*-[Trp-Ala-Gly-ψ(triazole)-Val-Ala] (**4**) was prepared in solution by applying the backbone amide linkage strategy and was used to study the impact of the replacement of an amide bond by a triazole linkage by extensive NMR analysis. Although a different hydrogen-bond pattern was observed, the NOE correlations in the specific β-turn were similar as in the parent compound. Biological testing and molecular modeling are still in progress. Moreover, a small library of triazole-containing cyclic tetrapeptides will be constructed by using the developed method.

Experimental Section

General: All reactions were conducted under nitrogen unless stated otherwise and monitored by TLC on silica gel coated aluminium sheets. Flash column chromatography was performed on silica gel 300–400 mesh using the indicated solvent mixtures. All solvents were distilled from sodium benzophenone ketyl (THF, Et_2O) or CaH_2 (DMF, CH_2Cl_2). The NMR spectra were determined in $CDCl_3$ solutions, using a Bruker ARX 400 and a Varian Inova 500 spectrometer unless indicated otherwise. Spectra are reported in δ units (ppm) and J values (Hz) with Me_4Si as the internal standard. HRMS spectra (FAB^+) were recorded with a JEOL JMS SX/SX 102A four-sector mass spectrometer. Infrared (IR) spectra were obtained with a Bruker IFS 28 FTIR spectrometer and are reported in wavenumbers (cm^{-1}). Melting points were recorded with a Büchi B-545 melting point apparatus and are uncorrected. HPLC analyses were measured with an Agilent HPLC system equipped with a C-18 column (Varian chrompack, inertsil-ODS-3, 3μ, 50 × 4.6 mm), a maximum flowspeed of 2.0 mL/min, the UV/Vis detector at λ = 220 nm or 254 nm as indicated, and a gradient of 100% A to 100% B [A: H_2O/CH_3CN/HCOOH (95:5:0.04); B: H_2O/CH_3CN/HCOOH (5:95:0.04)] in 5 min as the eluent. Optical rotations were measured with a Perkin–Elmer 241 polarimeter in a 1-dm cell (2 mL) in the indicated solvent at the indicated concentration, temperature and wavelenght.

Abbreviations: DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DIC = *N*,*N*′-diisopropylcarbodiimide, DIPEA = diisopropylethylamine,

EDCI = *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide, HATU = *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium hexafluorophosphate, HOBt = 1-hydroxybenzotriazole, pybox = (*S*,*S*)-2,2'-(2,6-pyridinediyl)bis(4-isopropyl-2-oxazoline).

Benzyl 4-Bromobutanoate (11): The reaction was carried out using a Dean–Stark trap. 4-Bromobutyric acid (8.51 g, 51 mmol, 1 equiv.) was dissolved in cyclohexane (70 mL). Benzyl alcohol (6.8 mL, 66 mmol, 1.3 equiv.) and *p*TSA (0.97 g, 5.1 mmol, 0.1 equiv.) were added to the solution. The reaction mixture was heated to reflux and stirred overnight. Upon completion, the reaction mixture was cooled to room temperature and washed with saturated aqueous sodium hydrogen carbonate solution (40 mL) and brine (30 mL). The organic layer was dried with Na_2SO_4 and the solvent evaporated to provide the crude product. The purified product was obtained by vacuum distillation (1 Torr, 110 °C) as clear oil (12.84 g, 98%). IR (neat): $\tilde{\nu}$ = 1735, 1637, 1496, 1449, 1385, 1311, 1202, 1163, 1125, 966 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.33 (m, 5 H), 5.18 (s, 2 H), 3.47 (t, J = 6.4 Hz, 2 H), 2.58 (t, J = 7.2 Hz, 2 H), 2.2 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4, 135.9, 128.7, 128.4, 128.3, 66.5, 32.8, 32.5, 27.8 ppm. HRMS (FAB^+): calcd. for $C_{11}H_{14}BrO_2$ [MH^+] 257.0179; found 257.0177.

Benzyl 4-(4-Formyl-3-methoxyphenoxy)butanoate (12): The bromide **11** (5.14 g, 20 mmol, 1 equiv.) and 4-hydroxy-2-methoxybenzaldehyde (3.04 g, 20 mmol, 1 equiv.) were dissolved in DMF (60 mL). K_2CO_3 (2.77 g, 20 mmol, 1 equiv.) and KI (0.33 g, 2 mmol, 0.1 equiv.) were added, and the reaction mixture was stirred at 70 °C for 3 d. After cooling to room temperature, water (100 mL) was added and the mixture extracted with Et_2O (2 × 100 mL). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. Pentane (70 mL) and *i*PrOH (70 mL) were added to induce precipitation, after which the product was filtered off and obtained as a white solid (4.56 g, 70%); m.p. 71–73 °C. IR (neat): $\tilde{\nu}$ = 1734, 1676, 1602, 1500, 1462, 1392, 1264, 1205, 1165, 1110, 1029, 974 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 10.30 (s, 1 H), 7.81 (d, J = 8.7 Hz, 1 H), 7.38–7.34 (m, 5 H), 6.53 (dd, J = 8.7, J = 2.0 Hz, 1 H), 6.50 (d, J = 2.1 Hz, 1 H), 5.16 (s, 2 H), 4.11 (t, J = 6.1 Hz, 2 H), 3.90 (s, 3 H), 2.61 (t, J = 7.2 Hz, 2 H), 2.19 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.4, 172.8, 165.4, 163.6, 135.8, 130.8, 128.8, 128.3, 128.2, 119.0, 98.9, 98.3, 67.1, 66.4, 55.6, 30.6, 24.4 ppm. HRMS (FAB^+): calcd. for $C_{19}H_{21}O_5$ [MH^+] 329.1391; found 329.1389.

Benzyl 4-{3-Methoxy-4-[(prop-2-ynylamino)methyl]phenoxy}-butanoate (13): The aldehyde linker **12** (2.00 g, 6.1 mmol, 1 equiv.) was dissolved in THF (60 mL). Na_2SO_4 (13.9 g, 98 mmol, 16 equiv.) and propargylamine (0.48 mL, 6.8 mmol, 1.1 equiv.) were added. The reaction mixture was stirred at room temperature overnight. $NaBH(OAc)_3$ (7.83 g, 37 mmol, 6 equiv.) was added and the resulting mixture stirred at room temperature overnight. The reaction mixture was quenched with saturated potassium carbonate solution (100 mL). The aqueous layer was extracted with EtOAc (2 × 125 mL). The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated in vacuo. Purification was carried out by flash column chromatography [silica gel, ethyl acetate/petroleum ether (boiling range 40–65 °C), 1:1] to yield a light yellow oil (1.81 g, 80%). IR (neat): $\tilde{\nu}$ = 3292, 2939, 1733, 1614, 1584, 1506, 1458, 1290, 1257, 1201, 1163, 1094, 1037, 974, 832 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.36 (m, 5 H), 7.16 (d, J = 8.2 Hz, 1 H), 6.46 (d, J = 2.3 Hz, 1 H), 6.43 (dd, J = 8.2, J = 2.4 Hz, 1 H), 5.16 (s, 2 H), 4.03 (t, J = 6.1 Hz, 2 H), 3.82 (s, 5 H), 3.41 (d, J = 2.4 Hz, 2 H), 2.61 (t, J = 7.3 Hz, 2 H), 2.25 (t, J = 2.4 Hz, 1 H), 2.17–2.13 (m, 2 H), 1.68 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 159.3, 158.5, 135.8, 130.5, 128.4, 128.1, 128.0, 119.9, 104.2, 98.8, 82.2, 71.2, 66.5, 66.1, 55.1, 47.3, 37.2, 30.6, 24.5 ppm. RP-HPLC: t_r = 6.68 min (λ = 254 or 220 nm).

4-{3-Methoxy-4-[(prop-2-ynylamino)methyl]phenoxy}butanoic Acid (14): The linker **13** (0.63 g, 1.73 mmol, 1 equiv.) was dissolved in wet MeOH (15 mL). LiOH (0.08 g, 3.46 mmol, 2 equiv.) was added and the reaction mixture stirred at 50 °C for 3 d. Upon completion, the solvents were evaporated, and 0.44 g (92%) of product was obtained after flash column chromatography [silica gel, CH_2Cl_2/MeOH, 8:2]. IR (neat): $\tilde{\nu}$ = 2938, 1686, 1611, 1586, 1421, 1292, 1134, 1034, 979, 835 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.10–7.90 (m, 2 H), 7.04 (d, J = 8.2 Hz, 1 H), 6.34 (s, 1 H), 6.29 (d, J = 8.2 Hz, 1 H), 3.93–3.76 (m, 4 H), 3.70 (m, 3 H), 3.41 (m, 2 H), 2.31 (t, J = 6.8 Hz, 2 H), 2.25 (s, 1 H), 1.95 (t, J = 6.5 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, MeOD): δ = 180.4, 162.9, 160.4, 133.0, 114.8, 106.7, 99.9, 77.0, 68.8, 56.1, 47.1, 40.0, 36.9, 34.1, 26.8 ppm. HRMS (FAB^+): calcd. for $C_{15}H_{20}NO_4$ [MH^+] 278.1394; found 278.1397.

4-(3-Methoxy-4-{[(9*H*-fluoren-9-ylmethoxycarbonyl)(prop-2-ynyl)-amino]methyl}phenoxy)butanoic Acid (15): The amine **14** (0.44 g, 1.6 mmol, 1 equiv.) was dissolved in a 1:1 mixture of CH_2Cl_2/acetone (10 mL). DIPEA (0.53 mL, 3.2 mmol, 2 equiv.) and Fmoc-Cl (0.50 g, 1.76 mmol, 1.1 equiv.) were added. The reaction mixture was stirred at room temperature overnight. The solvents were evaporated, and the resulting residue was dissolved in EtOAc and water. The water layer was acidified until the pH was <7.0. The organic layer was washed with a 1 M solution of potassium hydrogen sulfate. The organic layer was dried with Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash column chromatography [silica gel, CH_2Cl_2/MeOH, 95:5] yielded the desired product (0.60 g, 76%). IR (neat): $\tilde{\nu}$ = 3290, 3066, 2941, 1704, 1613, 1507, 1451, 1418, 1291, 1239, 1201, 1133, 1036, 910, 835 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.79 (br. s, 1 H), 7.79–7.28 (m, 9 H), 6.47 (m, 2 H), 4.58–4.95 (m, 4 H), 4.16–4.02 (m, 5 H), 3.80 (s, 3 H), 2.62 (m, 2 H), 2.38 (br. s, 1 H), 2.13 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.1, 159.6, 158.4, 156.2, 143.9, 141.2, 127.6, 127.5, 127.0, 124.8, 120.0, 117.3, 104.7, 98.8, 79.9, 71.6, 66.6, 65.0, 55.3, 47.2, 44.5, 36.2, 30.5, 24.4 ppm. HRMS (FAB^+): calcd. for $C_{30}H_{30}NO_6$ [MH^+] 500.2075; found 500.2077.

Resin-Bonded 4-{3-Methoxy-4-[(prop-2-ynylamino)methyl]phenoxy}-butanamide (17): Compound **15** (0.502 g, 1 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (5 mL). HOBt (0.202 g, 1.5 mmol, 1 equiv.) and DIC (0.24 mL, 1.5 mmol, 1.5 equiv.) were added. The resulting mixture was added to AM-NH_2 resin (1.00 g, 0.98 mmol g^{-1}) which had previously been washed with CH_2Cl_2 (3 × 5 mL). The mixture was stirred at room temperature for 1.5 h. The resin was then filtered and washed with CH_2Cl_2 and MeOH. The coupling step was repeated with compound **15** (0.7 mmol). The remaining amine groups were capped by suspension of the resin in a solution of Ac_2O (2 mL), pyridine (3 mL) and CH_2Cl_2 (5 mL) for 30 min. The resin was suspended in 20 vol.-% piperidine/DMF solution (15 mL). The mixture was stirred at room temperature for 1.5 h. The resin was filtered and washed with DMF, CH_2Cl_2, MeOH and DMF. Kaiser test indicated the absence of free amine. Final loading (0.401 mmol g^{-1}) and yield (51%) of the resin were calculated according to the UV-Fmoc test.

Benzyl 4-(4-{[{(2*S*)-2-[(9*H*-Fluoren-9-ylmethoxycarbonyl)amino]-3-methylbutanoyl}(prop-2-ynyl)amino]methyl}-3-methoxyphenoxy)butanoate (18a): Fmoc-Val-OH (0.32 g, 0.94 mmol, 1.25 equiv.) was dissolved in CH_2Cl_2 (4 mL). HATU (0.44 g, 1.13 mmol, 1.5 equiv.) and DIPEA (0.19 mL, 1.32 mmol, 1.5 equiv.) were added, and the solution was stirred at room temperature for 20 min. The solution

was added to a flask charged with the linker **13** (0.27 g, 0.75 mmol, 1 equiv.) in CH_2Cl_2 (4 mL). The reaction mixture was stirred at room temperature overnight. Upon completion, the reaction mixture was diluted with Et_2O and washed with water (3 × 20 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo. Flash column chromatography [silica gel, ethyl acetate/petroleum ether (boiling range 40–65 °C), 1:2] yielded the desired product as colorless oil (0.50 g, 95%). $[\alpha]_D$ = –19.0 (*c* = 1.0, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3299, 2966, 1734, 1646, 1614, 1585, 1506, 1449, 1290, 1208, 1164, 1125, 1095, 1033, 974, 835 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 7.5 Hz, 2 H), 7.65–7.60 (m, 2 H), 7.43–7.30 (m, 8 H), 7.15 (d, *J* = 8.2 Hz, 0.3 H), 7.10 (d, *J* = 8.2 Hz, 0.7 H), 6.40–6.36 (m, 2 H), 5.77 (d, *J* = 8.9 Hz, 0.7 H), 5.60 (d, *J* = 8.9 Hz, 0.3 H), 5.14 (s, 2 H), 4.99–4.95 (m, 1 H), 4.81–4.72 (m, 1 H), 4.59–4.55 (m, 1 H), 4.45–4.31 (m, 2 H), 4.25–4.22 (m, 1 H), 3.96 (t, *J* = 6.0 Hz, 2 H), 3.77 (s, 1 H), 3.72 (s, 3 H), 3.65–3.60 (m, 1 H), 2.57 (t, *J* = 7.2 Hz, 2 H), 2.13–2.06 (m, 2 H), 1.61 (br. s, 3 H), 1.02 (d, *J* = 6.7 Hz, 3 H), 0.95 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ = 172.9, 171.6, 160.4, 159.0 (major), 158.8 (minor), 156.3, 144.0, 144.0, 141.3, 141.3, 135.9, 131.2, 130.6, 128.6, 128.3, 128.2, 127.7, 127.1, 125.3, 125.2, 125.2, 120.0, 120.0, 115.5, 104.8, 104.4, 99.1, 98.8, 71.7, 66.9, 66.7, 66.3, 56.0, 55.7, 55.3, 47.2, 47.2, 46.0, 33.2, 32.2, 31.6, 30.8, 30.8, 24.6; 24.6, 19.6, 17.0 ppm. HRMS (FAB^+): calcd. for $C_{42}H_{45}N_2O_7$ [MH^+] 689.3227; found 689.3226. RP-HPLC: t_r = 6.67 min (λ = 254 or 220 nm).

Resin-Bonded 4-(4-{[{(2*S*)-2-[(9*H*-Fluoren-9-ylmethoxycarbonyl)-amino]-3-methylbutanoyl}(prop-2-ynyl)amino]methyl}-3-methoxyphenoxy)butanamide (18b): Fmoc-Val-OH (0.611 g, 1.8 mmol, 3 equiv.) was dissolved in DMF (8 mL). HATU (1.05 g, 2.7 mmol, 4.5 equiv.) and DIPEA (0.45 mL, 2.7 mmol, 4.5 equiv.) were added, and the mixture was stirred for 30 min. The solution was added to resin **17**, and the mixture was stirred for 3 h. The resin was filtered and washed with DMF, CH_2Cl_2 and MeOH. The coupling step was then repeated to ensure that the reaction was completed. Kaiser test indicated the absence of free amine. Final loading (0.380 mmol g^{-1}) and yield (98%) of the resin were calculated according to the UV-Fmoc test.

Benzyl 4-[4-({[(2*S*)-2-{[(2*S*)-1-(9*H*-Fluoren-9-ylmethoxycarbonyl)-pyrrolidin-2-ylcarbonyl]amino}-3-methylbutanoyl](prop-2-ynyl)-amino}methyl)-3-methoxyphenoxy]butanoate (19a): Compound **18a** (0.557 g, 0.81 mmol, 1 equiv.) was dissolved in 20 vol.-% piperidine/DMF solution (3 mL). The mixture was stirred at room temperature for 1 h. The solvent was evaporated to yield the deprotected intermediate which was used without further purification. It was dissolved in CH_2Cl_2 (15 mL). Fmoc-Pro-OH (0.412 g, 1.23 mmol, 1.5 equiv.), HATU (0.478 g, 1.23 mmol, 1.5 equiv.) and DIPEA (0.20 mL, 1.23 mmol, 1.5 equiv.), premixed for 10 min in CH_2Cl_2 (5 mL), were added, and the mixture was stirred at room temperature overnight. The solution was diluted with Et_2O and the organic layer subsequently washed with water, saturated aqueous sodium hydrogen carbonate solution and a 1 M solution of potassium hydrogen sulfate. The organic layer was dried with Na_2SO_4, filtered, and concentrated in vacuo. The desired product (0.612 g, 95%) was obtained by flash column chromatography [silica gel, CH_2Cl_2/MeOH, 98:2] as colorless oil. $[\alpha]_D$ = –39.0 (*c* = 1.0, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3298, 2966, 1733, 1644, 1507, 1449, 1292, 1205, 1164, 1124, 1033, 975 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.69 (m, 5 H), 7.43–7.32 (m, 8 H), 6.73–7.10 (m, 2 H), 6.11–6.37 (m, 2 H), 5.10–5.18 (m, 1 H), 5.15 (s, 2 H), 4.45–4.72 (m, 2 H), 4.25–4.43 (m, 4 H), 4.12–4.22 (m, 1 H), 4.03–4.11 (m, 1 H), 3.72–3.87 (m, 2 H), 3.55–3.69 (m, 4 H), 3.15–3.37 (m, 1 H), 2.38–2.50 (m, 2 H), 1.80–2.17 (m, 6 H), 1.46–1.57 (m, 2 H), 0.72–0.90 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ = 174.9, 173.0, 171.7, 160.3, 159.0, 131.0, 130.4, 129.1, 128.7, 128.6, 128.3, 128.2, 128.0, 127.2, 127.1, 127.0, 126.7, 125.5, 124.4, 124.3, 124.0, 121.0, 119.7, 115.7, 107.8, 104.8, 104.4, 98.9, 71.4, 66.7, 66.3, 60.7, 60.5, 55.3, 45.0, 47.4, 47.3, 45.9, 43.4, 36.8, 33.2, 32.0, 31.4, 31.3, 31.1, 30.8, 26.3, 26.2, 26.2, 26.6, 24.5, 19.8, 17.1 ppm. HRMS (FAB^+): calcd. for $C_{47}H_{52}N_3O_8$ [MH^+] 786.3756; found 786.3754. RP-HPLC: t_r = 6.68 min (λ = 254 or 220 nm).

Resin-Bonded 4-[4-({[(2*S*)-2-{[(2*S*)-1-(9*H*-Fluoren-9-ylmethoxycarbonyl)pyrrolidin-2-ylcarbonyl]amino}-3-methylbutanoyl](prop-2-ynyl)amino}methyl)-3-methoxyphenoxy]butanamide (19b): Resin **18b** was suspended in 20 vol.-% piperidine/DMF solution (15 mL). The mixture was stirred at room temperature for 1.5 h. The resin was filtered and washed with DMF, CH_2Cl_2, MeOH and DMF. Fmoc-Pro-OH (0.506 g, 1.5 mmol, 3 equiv.) was dissolved in DMF (8 mL). HATU (0.855 g, 2.25 mmol, 4.5 equiv.) and DIPEA (0.4 mL, 2.25 mmol, 4.5 equiv.) were added, and the mixture was stirred for 30 min. The solution was added to the resin and the mixture stirred for 3 h. The resin was filtered and washed with DMF, CH_2Cl_2 and MeOH. The coupling step was then repeated to ensure that the reaction was completed. Kaiser test indicated the absence of free amine. Final loading (0.334 mmol g^{-1}) and yield (91%) of the resin were calculated according to the UV-Fmoc test.

Benzyl 4-[4-({[(2*S*)-2-{[(2*S*)-1-{2-Azido-3-[4-(benzyloxy)phenyl]-propanoyl}pyrrolidin-2-ylcarbonyl]amino}-3-methylbutanoyl](prop-2-ynyl)amino}methyl)-3-methoxyphenoxy]butanoate (20a): Compound **19a** (0.62 g, 0.78 mmol, 1 equiv.) was dissolved in 20 vol.-% piperidine/DMF solution (3 mL). The mixture was stirred at room temperature for 1 h. The solvent was evaporated to yield the deprotected intermediate which was used without further purification. It was dissolved in CH_2Cl_2 (5 mL) and the solution cooled to 0 °C. N_3-Tyr-OH (0.276 g, 0.93 mmol, 1.2 equiv.), HOBt (0.114 g, 0.85 mmol, 1.1 equiv.) and EDCI (0.163 g, 0.85 mmol, 1.1 equiv.) were added, and the mixture was stirred overnight. The solution was diluted with Et_2O and the organic layer subsequently washed with water, saturated aqueous sodium hydrogen carbonate solution and a 1 M solution of potassium hydrogen sulfate. The organic layer was dried with Na_2SO_4, filtered, and concentrated in vacuo. The desired product, a light yellow oil (0.407 g, 62%), was obtained by flash column chromatography [silica gel, CH_2Cl_2/MeOH, 98:2]. $[\alpha]_D$ = –43.5 (*c* = 1.0, CH_2Cl_2/MeOH, 95:5). IR (neat): $\tilde{\nu}$ = 2105, 1734, 1648, 1510, 1242 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.37 (m, 10 H), 7.23–7.05 (m, 4 H), 6.98–6.94 (m, 4 H), 6.43 (m, 2 H), 5.16 (s, 2 H), 5.08 (d, *J* = 5.6 Hz, 3 H), 4.73–4.53 (m, 2 H), 4.01–4.3.91 (m, 4 H), 3.80–3.52 (m, 4 H), 3.43–3.06 (m, 3 H), 2.60–2.58 (m, 3 H), 2.20–2.13 (m, 7 H), 0.99–0.92 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ = 173.1, 171.6, 171.4, 170.9, 170.8, 169.0, 168.4, 160.5, 159.1, 158.0, 136.0, 130.4, 129.4, 129.0, 128.9, 128.7, 128.4, 128.1, 127.6, 127.4, 127.1, 126.8, 125.6, 121.1, 119.9, 119.7, 115.7, 115.3, 115.2, 105.0, 104.6, 99.1, 79.4, 71.7, 70.1, 66.9, 66.5, 61.9, 61.9, 60.8, 56.9, 55.4, 55.3, 55.0, 54.0, 47.3, 46.0, 43.5, 36.2, 33.2, 32.3, 30.8, 28.7, 25.1, 24.6, 19.7, 17.3 ppm. HRMS (FAB^+): calcd. for $C_{48}H_{55}N_6O_8$ [MH^+] 843.4081; found 843.4072. RP-HPLC: t_r = 6.50 min (λ = 254 or 220 nm).

Resin-Bonded 4-[4-({[(2*S*)-2-{[(2*S*)-1-{2-Azido-3-[4-(benzyloxy)phenyl]propanoyl}pyrrolidin-2-ylcarbonyl]amino}-3-methylbutanoyl]-(prop-2-ynyl)amino}methyl)-3-methoxyphenoxy]butanamide (20b): Resin **19b** was suspended in 20 vol.-% piperidine/DMF solution (15 mL). The mixture was stirred at room temperature for 1.5 h. The resin was filtered and washed with DMF, CH_2Cl_2, MeOH and DMF. N_3-Tyr(OBn)-OH (0.297 g, 1.0 mmol, 2 equiv.) was dis-

solved in CH_2Cl_2 (8 mL) and cooled to 0 °C. HOBt (0.304 g, 2.25 mmol, 4.5 equiv.) and DIC (0.35 mL, 2.25 mmol, 4.5 equiv.) were added. The solution was added to the resin and the mixture stirred at 0 °C for 3 h. The resin was filtered and washed with CH_2Cl_2, MeOH and Et_2O. The coupling step was then repeated to ensure that the reaction was completed. Kaiser test indicated the absence of free amine. Final loading (0.332 mmol g^{-1}) and yield (87%) of the resin were calculated by weighing. IR (neat): $\tilde{\nu}$ = 2104 cm^{-1}.

***cyclo*-[Pro-Val-*N*-linker-Gly-Ψ(triazole)-Tyr(OBn)] (21a):** Compound **20a** (0.084 g, 0.1 mmol, 1 equiv.) was dissolved in toluene (100 mL). DBU (0.05 mL, 0.3 mmol, 3 equiv.) was added and the solution degassed with argon for 30 min. The reaction mixture was heated to reflux while flushing with argon. At reflux, CuBr (0.003 g, 0.02 mmol, 0.2 equiv.) was added and the reaction mixture stirred at reflux overnight. The reaction mixture was cooled to room temperature and filtered through a Celite pad. The Celite pad was washed with MeOH. The filtrate was concentrated in vacuo to yield the crude product. Purification was carried out by flash column chromatography [silica gel, CH_2Cl_2/MeOH, 95:5] to provide the desired product as light yellow oil (0.032 g, 40%). IR (neat): $\tilde{\nu}$ = 2924, 1739, 1645, 1510, 1455, 1260, 1022 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.25 (m, 13 H), 7.01–6.82 (m, 5 H), 6.52–6.49 (m, 1 H), 5.16–5.00 (m, 7 H), 4.12–4.02 (m, 2 H), 3.74–3.51 (m, 7 H), 3.00–2.96 (m, 2 H), 2.42 (m, 1 H), 2.20–2.01 (m, 2 H), 1.87–1.53 (m, 4 H), 1.43–1.28 (m, 4 H), 0.88–0.76 (m, 6 H) ppm. HRMS (FAB^+): calcd. for $C_{48}H_{55}N_6O_8$ [MH^+] 843.4083; found 843.4083. RP-HPLC: t_r = 6.01 min (λ = 254 or 220 nm).

(2*S*)-1-[(2*S*)-2-Azido-3-(4-benzyloxyphenyl)propanoyl]-*N*-{(1*S*)-2-methyl-1-[(prop-2-ynylamino)carbonyl]propyl}pyrrolidine-2-carboxamide (22): Resin **20b** (0.124 g) was suspended in TFA (5 mL) and anisole (0.5 mL). The solution was stirred at room temperature for 2 h. The solvents were filtered off, and the resin was washed with TFA (5 mL), CH_2Cl_2 (3 × 5 mL) and MeOH (3 × 5 mL). The washings were collected and concentrated to yield the crude product (0.023 g, 53%). $[\alpha]_D$ = –37.6 (c = 0.66, CH_2Cl_2/MeOH, 95:5). IR (neat): $\tilde{\nu}$ = 3292, 2964, 2106, 1655, 1512, 1451, 1177 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.51–7.31 (m, 5 H), 7.17 (d, J = 8.8 Hz, 2 H), 7.01 (d, J = 8.4 Hz, 1 H), 6.94 (d, J = 8.6 Hz, 2 H), 6.01 (t, J = 5.6 Hz, 1 H), 4.61 (m, 1 H), 4.21 (m, 1 H), 4.05 (m, 2 H), 3.93 (m, 1 H), 3.61–3.38 (m, 2 H), 3.26–3.04 (m, 3 H), 2.29–1.91 (m, 6 H), 0.93 (d, J = 6.8 Hz, 3 H), 0.89 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, MeOD, mixture of rotamers): δ = 174.0, 173.6, 173.4, 170.9, 155.6, 155.4, 143.0, 142.8, 142.6, 132.5, 132.4, 131.3, 130.7, 129.9, 129.5, 129.3, 128.9, 128.6, 127.6, 126.8, 116.4, 116.2, 72.3, 72.2, 64.9, 63.5, 62.2, 61.6, 60.3, 55.6, 46.2, 38.4, 37.2, 36.6, 35.7, 32.8, 32.3, 30.8, 30.4, 25.9, 23.3, 19.7, 19.0, 18.9 ppm. HRMS (FAB^+): calcd. for $C_{29}H_{35}N_6O_4$ [MH^+] 531.2722; found 531.2720. RP-HPLC: t_r = 4.78 min (λ = 254 or 220 nm).

***cyclo*-[Pro-Val-Gly-Ψ(triazole)-Tyr(OBn)] (23):** To a solution of **22** (0.039 mmol, 1 equiv.) in toluene (40 mL) was added DBU (0.12 mmol, 3 equiv.). The solution was degassed with argon for 30 min and then heated to reflux while flushing with argon. At reflux, CuBr (0.031 mmol, 0.8 equiv.) was added and the solution stirred at reflux under argon overnight. The mixture was cooled to room temperature and filtered through a pad of Celite. The Celite pad was washed with CH_2Cl_2 (3 × 30 mL) and the filtrate concentrated in vacuo to provide a brown oil. Flash column chromatography [silica gel, CH_2Cl_2/MeOH, 97:3] eluted the product (0.009 g, 43%) as a white amorphous solid. $[\alpha]_D$ = –22.9 (c = 0.32, CH_2Cl_2/MeOH, 95:5). IR (neat): $\tilde{\nu}$ = 3307, 2922, 2851, 1659, 1512, 1451, 1242, 1179, 1110, 1025, 822 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.18 (s, 1 H), 7.47–7.28 (m, 5 H), 7.14 (d, J = 8.6 Hz, 2 H), 6.94 (d, J = 8.6 Hz, 2 H), 6.76 (m, 1 H), 6.55 (d, J = 9.2 Hz, 1 H), 5.82 (t, J = 7.6 Hz, 1 H), 5.16–5.02 (m, 1 H), 5.01 (s, 2 H), 4.94 (dd, J = 7.6, J = 15.2 Hz, 1 H), 4.58–4.48 (m, 1 H), 4.31–4.22 (m, 1 H), 4.14 (t, J = 8.0 Hz, 1 H), 3.73–3.61 (m, 1 H), 3.60–3.25 (m, 2 H), 2.21–1.55 (m, 5 H), 0.95 (d, J = 6.8 Hz, 3 H), 0.78 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 170.7, 167.7, 158.2, 136.8, 130.0, 128.7, 128.6, 128.0, 127.5, 125.4, 115.5, 69.9, 62.8, 61.8, 58.5, 48.0, 37.8, 35.5, 29.7, 29.5, 28.7, 24.8, 19.7, 18.0 ppm. HRMS (FAB^+): calcd. for $C_{29}H_{35}N_6O_4$ [MH^+] 531.2722; found 531.2723. RP-HPLC: t_r = 5.5 min (λ = 254 or 220 nm).

***cyclo*-[Pro-Val-Gly-Ψ(triazole)-Tyr] (2):** The benzyl-protected cyclic peptide **23** (0.01 mmol, 1 equiv.) was dissolved in MeOH (0.5 mL) and CH_2Cl_2 (4.5 mL). 5% Pd/C (50 wt.-%, 0.003 g) was added and the resulting mixture subjected to a three-cycle of vacuum and H_2 and stirred at room temperature under H_2 (balloon) overnight. The catalyst was removed by filtration through a pad of Celite and the filtrate concentrated in vacuo to afford the cyclic peptide (0.003 g, 73%) as a white solid. M.p. 188–193 °C. $[\alpha]_D$ = –33.0 (c = 0.2, CH_2Cl_2/MeOH, 95:5). IR (neat): $\tilde{\nu}$ = 3390, 2925, 2853, 1653, 1560, 1518, 1456, 1263, 1131, 1007, 984, 830 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$/MeOD, 955): δ = 8.20 (s, 1 H), 7.68 (br. s, 1 H), 7.13 (br. s, 1 H), 6.97 (d, J = 8.4 Hz, 2 H), 6.71 (d, J = 7.6 Hz, 2 H), 5.77 (t, J = 7.6 Hz, 1 H), 4.88 (d, J = 15 Hz, 1 H), 4.47 (t, J = 5.6 Hz, 1 H), 4.17 (d, J = 15.6 Hz, 2 H), 4.05 (d, J = 8.0 Hz, 1 H), 3.78–3.30 (m, 4 H), 2.18–1.50 (m, 5 H), 0.93 (d, J = 6.8 Hz, 3 H), 0.79 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, MeOD): δ = 173.4, 173.4, 168.6, 157.6, 147.5, 131.2, 127.9, 127.0, 116.5, 65.4, 62.8, 61.0, 38.5, 33.0, 31.1, 27.8, 26.0, 23.7, 19.7, 19.1 ppm. HRMS (FAB^+): calcd. for $C_{22}H_{29}N_6O_4$ [MH^+] 441.2252; found major peak at 881.4 (as dimeric artefact).[22]

Benzyl 4-(4-{[{(2*S*)-2-[(9*H*-Fluoren-9-ylmethoxycarbonyl)amino]propanoyl](prop-2-ynyl)amino]methyl}-3-methoxyphenoxy)butanoate (24): Compound **13** (0.551 g, 1.5 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (15 mL). Fmoc-Ala-OH (0.584 g, 1.88 mmol, 1.25 equiv.), HOBT (0.431 g. 2.25 mmol, 1.5 equiv.) and EDCI (0.304 g, 2.25 mmol, 1.5 equiv.) were added to the solution. The reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc (30 mL) and the organic layer washed with water, saturated aqueous sodium hydrogen carbonate solution and a 1 M solution of potassium hydrogen sulfate. The organic layer was dried with Na_2SO_4, filtered, and concentrated in vacuo. Flash column chromatography [silica gel, CH_2Cl_2/MeOH, 98:2] yielded the pure compound as colorless oil (0.699 g, 70%). $[\alpha]_D$ = –13.9 (c = 1.0, CH_2Cl_2/MeOH, 95:5). IR (neat): $\tilde{\nu}$ = 3299, 2943, 1732, 1651, 1614, 1507, 1454, 1295, 1256, 1208, 1165, 1032, 975, 834 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ = 7.80 (d, J = 7.5 Hz, 2 H), 7.65 (d, J = 7.0 Hz, 2 H), 7.44–7.32 (m, 9 H), 7.18 (d, J = 8.2 Hz, 0.3 H), 7.12 (d, J = 7.9 Hz, 0.7 H), 6.43–6.40 (m, 2 H), 5.93 (m, 1 H), 5.16 (s, 2 H), 5.10–5.06 (m, 1 H), 4.74–4.66 (m, 1 H), 4.50–4.46 (m, 2 H), 4.41–4.38 (m, 2 H), 4.27–4.23 (m, 1 H), 4.02–3.98 (m, 2 H), 3.80–3.76 (m, 4 H), 2.60 (t, J = 7.2 Hz, 2 H), 2.25–2.23 (m, 1 H), 2.22–2.11 (m, 2 H), 1.46–1.41 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ = 172.9, 172.5, 172.4, 160.4, 159.8, 158.9, 158.8, 155.5, 155.4, 144.0, 143.9, 141.3, 135.9, 131.1, 130.3, 128.6, 128.3, 128.2, 127.7, 127.0, 125.2, 120.0, 116.8, 115.3, 104.9, 104.5, 99.1, 98.9, 78.7, 72.8, 71.9, 67.0, 66.8, 66.8, 66.7, 66.3, 55.3, 55.2, 53.8, 47.2, 45.7, 43.8, 36.6, 33.4, 30.8, 30.7, 29.3, 24.6, 24.6, 19.7, 19.4 ppm. HRMS (FAB^+): calcd. for $C_{40}H_{41}N_2O_7$ [MH^+] 661.2916; found 661.2917. RP-HPLC: t_r = 6.46 min (λ = 254 or 220 nm).

Benzyl 4-[4-({[(2*S*)-2-({[(2*S*)-3-[1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl]-2-[(9*H*-fluoren-9-ylmethoxycarbonyl)amino]propanoyl}amino)pro-

panoyl](prop-2-ynyl)amino}methyl)-3-methoxyphenoxy]butanoate (25): Compound **24** (0.660 g, 1.0 mmol, 1 equiv.) was dissolved in a 20 vol.-% piperidine/DMF solution (2.5 mL). The mixture was stirred at room temperature for 2 h. The solvents were evaporated to yield the deprotected intermediate which was used without further purification. It was dissolved in dry CH_2Cl_2 (10 mL). Fmoc-Trp(Boc)-OH (0.658 g, 1.25 mmol, 1.25 equiv.), HOBt (0.287 g, 1.5 mmol, 1.5 equiv.) and EDCI (0.203 g, 1.5 mmol, 1.5 equiv.) were added to the solution. The reaction mixture was stirred at room temperature overnight. The mixture was diluted with Et_2O (20 mL) and the organic layer washed with water, saturated aqueous sodium hydrogen carbonate solution and a 1 M solution of potassium hydrogen sulfate. The organic layer was dried with Na_2SO_4, filtered, and concentrated in vacuo. Flash column chromatography [silica gel, CH_2Cl_2 followed by CH_2Cl_2/MeOH, 98:2] yielded the pure compound as colorless oil (0.654 g, 69%). $[\alpha]_D$ = –12.9 (c = 1.0, CH_2Cl_2/MeOH, 95:5). IR (neat): $\tilde{\nu}$ = 3299, 1729, 1639, 1541, 1506, 1452, 1371, 1260, 1161, 1087, 1038, 831 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.16 (m, 1 H), 7.79 (d, J = 7.5 Hz, 2 H), 7.66–7.56 (m, 4 H), 7.53–7.21 (m, 11 H), 7.09–7.06 (m, 2 H), 6.43–6.41 (m, 2 H), 5.57–5.55 (m, 1 H), 5.21 (m, 1 H), 5.16–5.15 (m, 2 H), 4.69–4.65 (m, 2 H), 4.49–4.37 (m, 4 H), 4.23–4.22 (m, 1 H), 4.03–3.96 (m, 2 H), 3.77–3.65 (m, 4 H), 3.22–3.18 (m, 2 H), 2.63–2.56 (m, 2 H), 2.21–2.12 (m, 3 H), 1.67 (m, 9 H), 1.35–1.31 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ = 173.0, 171.8, 171.6, 169.9, 169.7, 160.4, 159.8, 158.8, 155.9, 149.5, 143.9, 143.7, 141.3, 135.9, 135.5, 130.4, 130.3, 128.6, 128.3, 128.2, 127.7, 127.1, 125.2, 124.6, 124.5, 122.8, 120.0, 119.0, 119.0, 116.6, 115.4, 115.3, 115.1, 104.8, 104.5, 99.1, 98.8, 83.6, 78.6, 72.9, 71.9, 67.3, 66.7, 66.7, 66.4, 66.3, 55.3, 55.1, 47.2, 47.1, 46.0, 45.9, 45.5, 43.7, 36.5, 33.3, 30.8, 28.2, 24.6, 19.2, 18.9 ppm. HRMS (FAB^+): calcd. for $C_{56}H_{59}N_4O_{10}$ [MH^+] 947.4231; found 947.4229. RP-HPLC: t_r = 6.92 min (λ = 254 or 220 nm).

Benzyl 4-[4-({[(2*S*)-2-({(2*S*)-3-[1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl]-2-({(2*S*)-2-[(9*H*-fluoren-9-ylmethoxycarbonyl)amino]propanoyl}-amino)propanoyl}amino)propanoyl](prop-2-ynyl)amino}methyl)-3-methoxyphenoxy]butanoate (26): Compound **25** (0.615 g, 0.65 mmol, 1 equiv.) was dissolved in 20 vol.-% piperidine/DMF solution (2.0 mL). The mixture was stirred at room temperature for 2 h. The solvents were evaporated to yield the deprotected intermediate which was used without further purification. It was dissolved in dry CH_2Cl_2 (10 mL). Fmoc-Ala-OH (0.253 g, 0.81 mmol, 1.25 equiv.), HOBt (0.132 g, 0.98 mmol, 1.5 equiv.) and EDCI (0.132 g, 0.98 mmol, 1.5 equiv.) were added to the solution. The reaction mixture was stirred at room temperature overnight. The mixture was diluted with Et_2O and the organic layer washed with water, saturated aqueous sodium hydrogen carbonate solution and a 1 M solution of potassium hydrogen sulfate. The organic layer was dried with Na_2SO_4, filtered, and concentrated in vacuo. Flash column chromatography [silica gel, CH_2Cl_2 followed by CH_2Cl_2/MeOH, 98:2] yielded the pure compound as a white foam (0.444 g, 67%). $[\alpha]_D$ = –17.1 (c = 1.0, CH_2Cl_2/MeOH, 95:5). IR (neat): $\tilde{\nu}$ = 3295, 2931, 1729, 1653, 1506, 1450, 1376, 1256, 1208, 1160, 1083 cm^{-1}. ^1H NMR (100 MHz, $CDCl_3$): δ = 8.12 (m, 1 H), 7.78 (d, J = 7.2 Hz, 2 H), 7.63–7.58 (m, 4 H), 7.41–7.28 (m, 8 H), 7.26–7.16 (m, 1 H), 7.08–7.05 (m, 2 H), 6.87 (br. s, 1 H), 6.42–6.40 (m, 2 H), 5.47 (br. s, 1 H), 5.16 (s, 2 H), 4.82 (m, 1 H), 4.48–4.21 (m, 4 H), 4.01–3.99 (m, 3 H), 3.76 (s, 1 H), 3.68 (s, 3 H), 3.31–3.27 (m, 2 H), 2.62–2.59 (m, 2 H), 2.20–2.14 (m, 3 H), 1.86–1.70 (m, 2 H), 1.66–1.56 (m, 9 H), 1.40 (m, 3 H), 1.29 (br. s, 3 H), 1.29 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ = 173.0, 172.2, 171.7, 169.5, 169.3, 160.4, 159.8, 158.9, 158.8, 155.9, 149.6, 143.9, 143.8, 141.3, 135.9, 135.4, 131.0, 130.4, 130.4, 128.6, 128.3, 128.3, 127.7, 127.1, 125.2, 124.6, 122.7, 120.0, 119.1, 119.0, 116.7, 115.3, 115.2, 115.1, 104.9, 104.5, 99.1, 98.8, 83.7, 78.7, 72.9, 71.9, 67.1, 66.8, 66.4, 55.4, 55.1, 53.3, 50.7, 47.1, 46.9, 46.0, 45.9, 44.6, 42.8, 39.8, 35.6, 32.4, 29.9, 27.3, 27.0, 25.7, 24.2, 23.9, 23.7, 18.2, 18.0 ppm. HRMS (FAB^+): calcd. for $C_{59}H_{64}N_5O_{11}$ [MH^+] 1018.4602; found 1018.4598. RP-HPLC: t_r = 6.50 min (λ = 254 or 220 nm).

Benzyl 4-[4-({[(2*S*)-2-{[(2*S*)-3-[1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl]-2-{[(2*S*)-2-{[(2*R*)-2-azido-3-methylbutanoyl]amino}propanoyl]-amino}propanoyl]amino}propanoyl](prop-2-ynyl)amino}methyl)-3-methoxyphenoxy]butanoate (27): Compound **26** (0.408 g, 0.4 mmol, 1 equiv.) was dissolved in 20 vol.-% piperidine/DMF solution (2.0 mL). The mixture was stirred at room temperature for 1 h. The solvents were evaporated to yield the deprotected intermediate which was used without further purification. It was dissolved in CH_2Cl_2 (7.5 mL). The solution was cooled to 0 °C. N_3-Val-OH (0.072 g, 0.5 mmol, 1.25 equiv.), HOBt (0.115 g, 0.6 mmol, 1.5 equiv.) and EDCI (0.081 g, 0.6 mmol, 1.5 equiv.) were added to the solution. The reaction mixture was stirred overnight. The mixture was diluted with Et_2O and the organic layer washed with water, saturated aqueous sodium hydrogen carbonate solution and a 1 M solution of potassium hydrogen sulfate. The organic layer was dried with Na_2SO_4, filtered, and concentrated in vacuo. Purification was carried out by flash column chromatography [silica gel, CH_2Cl_2 followed by CH_2Cl_2/MeOH, 98:2]. The desired compound was obtained as light yellow oil (0.293 g, 80%). $[\alpha]_D$ = –4.6 (c = 0.28, CH_2Cl_2/MeOH, 95:5). IR (neat): $\tilde{\nu}$ = 3296, 2968, 2099, 1732, 1508, 1454, 1369, 1256, 1160 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 8.11 (m, 1 H), 7.60–7.59 (m, 1 H), 7.49–7.48 (m, 1 H), 7.36–7.16 (m, 9 H), 7.07–7.05 (m, 3 H), 6.41–6.39 (m, 2 H), 5.21 (m, 1 H), 5.15 and 5.13 (s, 2 H), 4.85 (m, 1 H), 4.67–4.37 (m, 3 H), 4.01–3.97 (m, 2 H), 3.76 (s, 1 H), 3.69–3.65 (m, 4 H), 3.23–3.19 (m, 2 H), 2.61–2.58 (m, 2 H), 2.31–2.28 (m, 1 H), 2.21–2.08 (m, 3 H), 1.62–1.54 (m, 9 H), 1.38–1.27 (m, 6 H), 1.03 (d, J = 6.8 Hz, 3 H), 0.89 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, mixture of rotamers): δ = 173.0, 171.7, 169.4, 168.8, 160.8, 160.4, 159.8, 158.8, 158.7, 149.6, 135.9, 130.9, 130.4, 128.6, 128.3, 128.2, 124.6, 124.5, 122.6, 119.1, 119.0, 116.6, 115.2, 115.2, 115.1, 104.9, 104.5, 99.1, 98.8, 83.6, 78.7, 72.8, 71.9, 69.8, 66.8, 66.3, 55.3, 55.1, 53.3, 48.7, 46.8, 46.0, 45.8, 45.5, 43.6, 40.6, 36.4, 33.31, 28.2, 27.8, 26.6, 25.1, 24.7, 19.6, 19.5, 18.9, 18.5, 16.8 ppm. HRMS (FAB^+): calcd. for $C_{49}H_{61}N_8O_{10}$ [MH^+] 921.4511; found 921.4509. RP-HPLC: t_r = 6.50 min (λ = 254 or 220 nm).

***cyclo*-[Trp(Boc)-Ala-*N*-linker-Gly-Ψ(triazole)-Val-Ala] (28):** Ligand (*S*,*S*)-bis(4-isopropyl)pybox (0.003 g, 0.01 mmol, 0.4 equiv.) and CuBr (0.0008 g, 0.005 mmol, 0.2 equiv.) were dissolved in acetonitrile (5 mL), and the mixture was stirred at room temperature for 10 min. The linear peptide **27** (0.023 g, 0.025 mmol, 1 equiv.) was dissolved in acetonitrile (20 mL). DIPEA (0.013 mL, 0.075 mmol, 3 equiv.) and the pybox/CuBr solution were added, and the reaction mixture was stirred at room temperature overnight. After consumption of the starting material, the solvents were evaporated to yield a crude product. Flash column chromatography [silica gel, CH_2Cl_2/MeOH, 95:5] yielded 0.007 g (32%) of the desired product as light yellow oil. $[\alpha]_D$ = –7.0 (c = 0.75, CH_2Cl_2/MeOH, 95:5). IR (neat): $\tilde{\nu}$ = 2670, 1731, 1665, 1614, 1150, 1371, 1259, 1159, 1084, 1022 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, J = 7.9 Hz, 1 H), 7.87 (br. s, 1 H), 7.64 (d, J = 7.7 Hz, 1 H), 7.47–7.10 (m, 9 H), 7.12 (d, J = 8.8 Hz, 1 H), 6.92 (br. s, 1 H), 6.46 (m, 2 H), 5.16 (s, 2 H), 4.98–4.93 (m, 2 H), 4.69 (m, 1 H), 4.15–4.13 (m, 2 H), 4.03 (t, J = 6.1 Hz, 2 H), 3.90 (m, 1 H), 3.78 (s, 3 H), 3.57–3.49 (m, 1 H), 3.32–3.23 (m, 1 H), 2.63–2.59 (m, 3 H), 2.19–2.12 (m, 3 H), 1.66 (m, 9 H), 1.37 (d, J = 6.9 Hz, 3 H), 1.27 (d, J = 7.1 Hz, 5

H), 1.14 (d, J = 6.6 Hz, 3 H), 0.89 (d, J = 6.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2, 172.5, 170.5, 167.8, 160.4, 158.9, 149.6, 136.1, 135.7, 130.4, 130.0, 128.8, 128.5, 128.4, 125.0, 124.7, 123.0, 119.2, 116.7, 115.9, 115.6, 104.8, 99.4, 83.9, 71.6, 67.0, 66.6, 57.2, 55.5, 50.8, 47.3, 47.1, 45.7, 40.9, 30.9, 30.7, 29.9, 29.5, 28.4, 26.8, 26.0, 25.3, 24.9, 24.8, 19.4, 19.1, 18.2, 17.0 ppm. HRMS (FAB$^+$): calcd. for $C_{49}H_{61}N_8O_{10}$ [MH$^+$] 921.4511; found 921.4512. RP-HPLC: t_r = 6.20 min (λ = 254 or 220 nm).

***cyclo*-[Trp-Ala-Gly-Ψ(triazole)-Val-Ala] (4):** The cyclic pentapeptide **28** (0.017 g, 0.018 mmol) was dissolved in TFA (2.5 mL) and anisole (0.25 mL). The reaction mixture was stirred at room temperature overnight. The solvents were evaporated. Cold Et_2O was added to the residue and the precipitate filtered off. The desired product was obtained as a white solid (0.006 g, 65%). $[a]_D$ = –5.9 (c = 0.31, CH_2Cl_2/MeOH, 95:5). IR (neat): $\tilde{\nu}$ = 3283, 1668, 1532, 1454, 1203, 1138, 1056 cm^{-1}. ^{1}H NMR (400 MHz, [D$_5$]pyridine): δ = 11.90 (s, 1 H), 9.75 (d, J = 7.6 Hz, 1 H), 9.53 (d, J = 7.2 Hz, 1 H), 9.32 (d, J = 7.6 Hz, 1 H), 9.15 (m, 1 H), 8.66 (s, 1 H), 7.94 (d, J = 8.0 Hz, 1 H), 7.54 (d, J = 8.1 Hz, 1 H), 7.41 (d, J = 2.1 Hz, 1 H), 7.25 (m, 1 H), 7.09 (t, J = 7.4 Hz, 1 H), 5.48 (AX part of ABX system, J_{AB} = 15.1, J_{AX} = 8.0, J_{BX} = 3.3 Hz, 1 H), 5.27 (d, J = 10.9 Hz, 1 H), 4.86 (m, 1 H), 4.64 (t, J = 7.4 Hz, 1 H), 4.53 (AB part of ABX system, J_{AB} = 15.1, J_{AX} = 8.0, J_{BX} = 3.3 Hz, 1 H), 4.37 (t, J = 7.0 Hz, 1 H), 3.82 (AB part of ABX system, J_{AB} = 13.9, J_{AX} = 7.2, J_{BX} = 7.1 Hz, 2 H), 2.95 (m, 1 H), 1.73–1.71 (m, 6 H), 1.67 (d, J = 6.6 Hz, 3 H), 0.78 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_5$]pyridine): δ = 173.3, 172.5, 172.4, 168.9, 148.3, 137.8, 128.7, 125.1, 122.3, 122.2, 119.7, 112.3, 111.2, 72.5, 57.1, 53.5, 51.1, 36.1, 30.6, 29.2, 19.9, 19.3, 18.2, 16.9 ppm. HRMS (FAB$^+$): calcd. for $C_{25}H_{33}N_8O_4$ [MH$^+$] 509.2627; found 509.2628.

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