Stereoselective Synthesis of Protected Peptides Containing an *anti* β-Hydroxy Tyrosine

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Abstract: Protected peptides containing an *anti* β-hydroxy tyrosine are synthesized in a straightforward and highly efficient manner through the direct and stereoselective addition of *N*-azidoacetyl-4-isopropyl-1,3-thiazolidine-2-thione to dialkyl acetals catalyzed by a nickel(II) complex, the forging of an amide bond by removal of the chiral auxiliary with an amino ester, and final coupling with a third amino acid.

Introduction

β-Hydroxy tyrosine is a nonproteinogenic amino acid present in a variety of cyclic peptides and depsipeptides[1] with remarkable biological activity such as vancomycin[2] or callipeltins[3] (Figure 1). Obtaining these substrates thus requires the stereoselective synthesis and suitable protection of the desired β-hydroxy tyrosine stereoisomer[4–7] followed by the coupling with the other residues of the peptidic sequence. Notably, the latter step often turns out to be troublesome and requires special and increasingly sophisticated coupling reagents[8] that permit the assembly of the different amino acids without causing epimerization of the Cα position or any other side reactions.[9] Thus, it goes without saying that if both the synthetic and the coupling steps could be merged in some way, the overall process would be much more efficient.

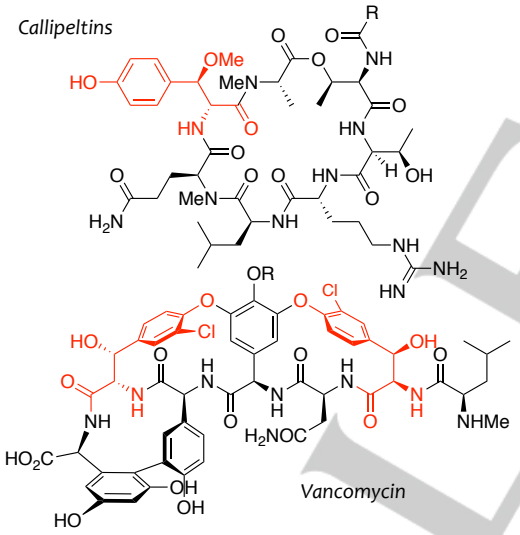
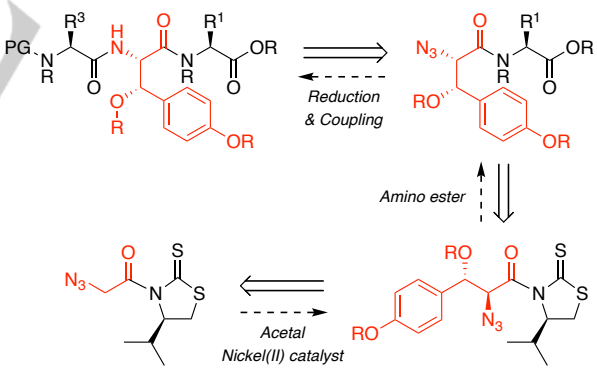


Figure 1. Metabolites containing an *anti* β-hydroxy tyrosine.

Faced with this challenge, we envisaged that tripeptide fragments containing an *anti* β-alkoxy tyrosine might be prepared through (i) the direct and stereocontrolled reaction of chiral *N*-azidoacetyl-4-isopropyl-1,3-thiazolidine-2-thione with dialkyl acetals catalyzed by structurally simple and commercially available nickel(II) salts, and (ii) conversion of the resultant β-alkoxy-α-azido adducts into the corresponding dipeptides by simple treatment with the appropriate α-amino acid (Scheme 1).[10] Thereby, the 4-isopropyl-1,3-thiazolidine-2-thione[11,12] would act as a chiral template[13,14] but also as a coupling reagent.[15] In turn, (iii) reduction of the azido group followed by (iv) the forging of a further amide linkage would give the desired tripeptide in a straighforward, stereocontrolled, and highly efficient manner (Scheme 1). Herein, we disclose the implementation of such a strategy and its application to the synthesis of a protected tripeptide with a central allyl-protected *anti* β-hydroxy tyrosine, which is structurally close to a fragment of vancomycin.



Scheme 1. Retrosynthetic analysis of a protected tripeptide containing a central *anti* β-hydroxy tyrosine.

Results and Discussion

The azido group is currently considered as a masked amino group and has thus been exploited with a great success in a number of synthetic sequences. Unfortunately, metal enolates from α-azidocarbonyl compounds usually decompose into the corresponding imino derivatives, which prevent them from being used as surrogates for the amino acid glycine in the stereoselective construction of carbon-carbon bonds. As an exception, Franck found that treatment of chiral α-azidoacetyl thiazolidinethiones with stoichiometric amounts of $TiCl_4$/iPr_2NEt

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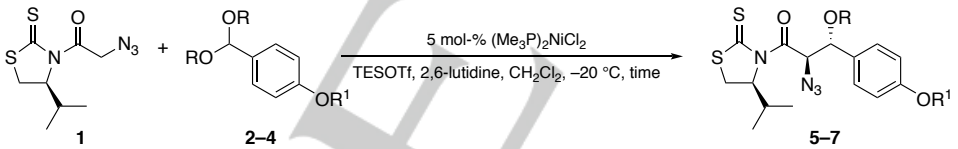
at low temperature afforded the corresponding titanium(IV) enolates, which underwent highly diastereoselective aldol reactions.[15a] More recently, Kumagai and Shibasaki have developed direct and asymmetric aldol and Mannich reactions from α-azido 7-azaindolinylamide catalyzed by a copper(I) complex.[6a,16] In turn, we have reported that chiral α-azidoacetyl thiazolidinethiones also participate in direct and stereoselective Lewis acid-mediated reactions with acetals catalyzed by nickel(II) complexes.[13] All together, these examples indicate that certain metal enolates of α-azido carboxylic compounds are stable enough to engage in the stereoselective construction of carbon–carbon bonds.

Thus, taking advantage of these precedents, we carefully assessed the reaction of (*S*) *N*-azidoacetyl-4-isopropyl-1,3-thiazolidine-2-thione (**1** in Table 1)[12] with dialkyl acetals from 4-alkoxybenzaldehydes (**2–4** in Table 1). Following a comprehensive evaluation of the experimental conditions for such substrates, we firmly established that the reaction of **1** with 1.1 equivalents of acetals **2–4** in the presence of 5 mol-% of commercially available and easy to handle $(Me_3P)_2NiCl_2$, 1.5 equivalents of TESOTf, and 1.5 equivalents of 2,6-lutidine at –20 °C for 3 h provides the *anti* adducts **5–7** in high yields and diastereoselectivities (*dr* > 95:5). Importantly, the outcome of such reactions was highly reproducible in up to 6 mmol scale (entries 6–8 in Table 1), so adducts **5–7** may be prepared in a gram scale after a short chromatographic purification.

Once we had reliable and efficient access to *anti* β-hydroxy tyrosine adducts, we next evaluated the removal of the chiral auxiliary.[15,17] As shown in Table 2, simple treatment of **5** with 1.1 equivalents of hydrochloric salts of representative amino esters **a–e** afforded the desired dipeptides in up to 96% yield without epimerization (*dr* > 95:5) after a short chromatographic purification.

Aiming to expand the scope of the process, we next examined the reaction with α-amino acids possessing a secondary amino group, like proline and pipecolic acid. Given that such reagents are less nucleophilic than their primary counterparts **a–e**, we first assessed the capability of methyl prolinate and pipecolate hydrochlorides (**f** and **g** respectively) to remove the chiral auxiliary of non–sterically hindered α-azidoacetyl thiazolidinethione **1** (Scheme 2). Gratifyingly, full conversion of **1** was observed when it was treated with **f** under the experimental conditions previously optimized for **a–e** (see Table 2) and the expected amide **9f** was isolated as a 5:1 mixture of rotamers with a 75% yield (Scheme 2). On the contrary, methyl pipecolate hydrochloride **g** turned out to be much less reactive and the displacement of the thiazolidinethione was incomplete after 4 h; thereby, amide **9g** was also obtained as a 5:1 mixture of rotamers but in a moderate yield of 40% and a large amount (42%) of unreacted starting material **1** was recovered (Scheme 2).

Table 1. Direct, stereoselective, and catalytic reaction of **1** with dialkyl acetals from 4-alkoxybenzaldehydes[a]

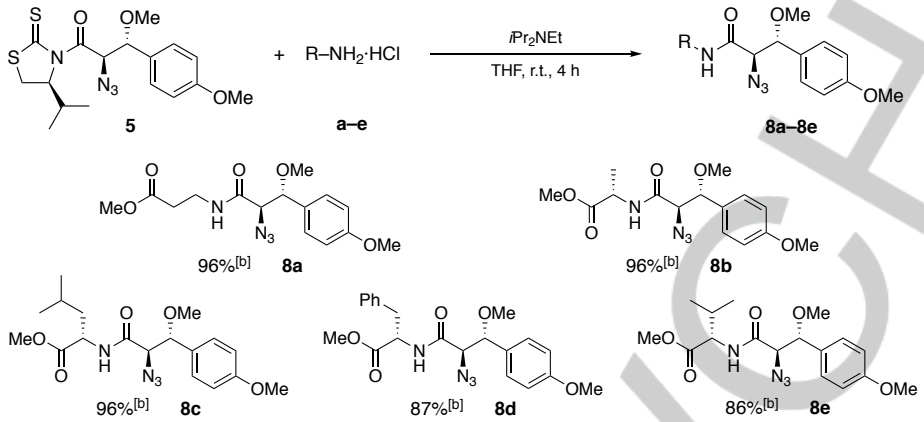


1 **2–4** **5–7**

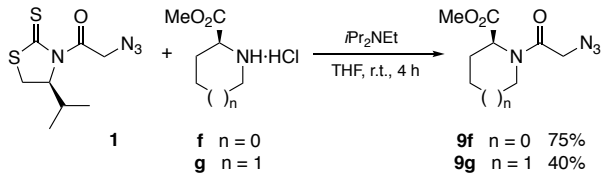
Entry	Acetal	R	R^1	Scale (mmol)	Equiv TESOTf	Time (h)	Adduct	*dr*[b]	Yield[c] (%)
1	**2**	Me	Me	0.5	1.2	15	**5**	> 95:5	60
2	**2**	Me	Me	0.5	1.5	15	**5**	> 95:5	86
3	**2**	Me	Me	0.5	2.2	15	**5**	> 95:5	84
4	**2**	Me	Me	0.5	1.5	3	**5**	> 95:5	84
5	**3**	Me	Bn	0.5	1.5	15	**6**	> 95:5	83
6	**3**	Me	Bn	0.5	1.5	3	**6**	> 95:5	82
7	**3**	Me	Bn	3	1.5	3	**6**	> 95:5	81
8	**3**	Me	Bn	6	1.5	3	**6**	> 95:5	82
9	**4**	Allyl	Bn	0.5	1.5	15	**7**	> 95:5	74
10	**4**	Allyl	Bn	0.5	1.5	3	**7**	> 95:5	77
11	**4**	Allyl	Bn	1	1.5	3	**7**	> 95:5	76

[a] The reaction was carried out from **1** (0.5 M in CH_2Cl_2), **2–4** (1.1 equiv), $(Me_3P)_2NiCl_2$ (5 mol-%), and 2,6-lutidine (1.5 equiv). [b] Diastereomeric ratio established by ^1H NMR analysis of the reaction mixture. [c] Yield of isolated product

Table 2. Removal of the chiral auxiliary with amino esters. Synthesis of dipeptides [a]



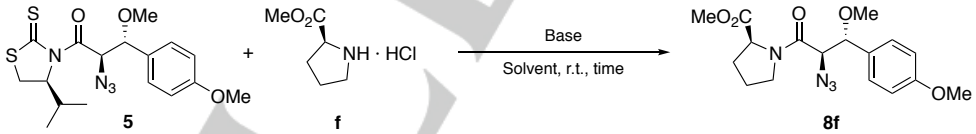
[a] The reaction was carried out from **5** (0.15 M in THF), **a–e** (1.1 equiv), and *i*Pr$_2$NEt (2 equiv) for 4 h. [b] Isolated yield.



Scheme 2. Reaction of **1** with methyl L-prolinate (**f**) and L-pipecolate (**g**).

Despite such preliminary results, a similar addition of methyl L-prolinate (**f**) to adduct **5** from the dimethyl acetal of *p*-anisaldehyde proved to be troublesome. Indeed, the same experimental conditions successfully applied to **1** afforded the desired dipeptide **8f** with a meager 33% yield (entry 1 in Table 3). The yield was improved after stirring overnight at r.t. (entry 2 in Table 3), but longer reaction times did not produce any further increase. Other bases did not improve these results either (compare entries 2–4 in Table 3). In turn, acetonitrile proved to be less suitable than THF, whereas CH_2Cl_2 afforded similar results (entries 5 and 6 in Table 3). Finally, it was found that the reaction with the amino ester instead of the hydrochloride counterpart performed better and afforded dipeptide **8f** as a single diastereomer (dr > 95:5) with a 69% yield after 4 h in the presence of 5 mol-% of DMAP or a 72% yield if 2.2 equivalents of methyl L-prolinate were used (entries 7 and 8 in Table 3).

Table 3. Removal of the chiral auxiliary of **5** with methyl L-prolinate[a]



Entry	Solvent	Base	Time (h)	Yield[b] (%)
1	THF	*i*Pr$_2$NEt	4	33
2	THF	*i*Pr$_2$NEt	16	58
3	THF	Et$_3$N	16	40
4	THF	2,6-lutidine	16	32
5	CH_3CN	*i*Pr$_2$NEt	16	30
6	CH_2Cl_2	*i*Pr$_2$NEt	16	60
7[c]	CH_2Cl_2	DMAP	4	69
8[d]	CH_2Cl_2	–	4	72

[a] The reaction was carried out from **5** (0.15 M), methyl L-prolinate hydrochloride **f** (1.1 equiv), and base (2 equiv). [b] Yield of isolated **8f**. [c] Methyl L-prolinate (1.1 equiv) and DMAP (5 mol-%) were used instead of **f**. [d] Methyl L-prolinate (2.2 equiv) was used instead of **f**.

However, in spite of our efforts, the reaction of **5** with methyl L-pipecolate (**g**) failed and the desired dipeptide was never isolated in synthetically useful yields. Likely, the steric hindrance of the substrate and the poor nucleophilic character of **g** prevent it from properly attacking the carbonyl bond of **5**.

Having established the scope of the process, we focused our attention on the synthesis of a peptidic fragment **10** structurally close to the east hemisphere of vancomycin (Figure 2) to test the potential of the method.

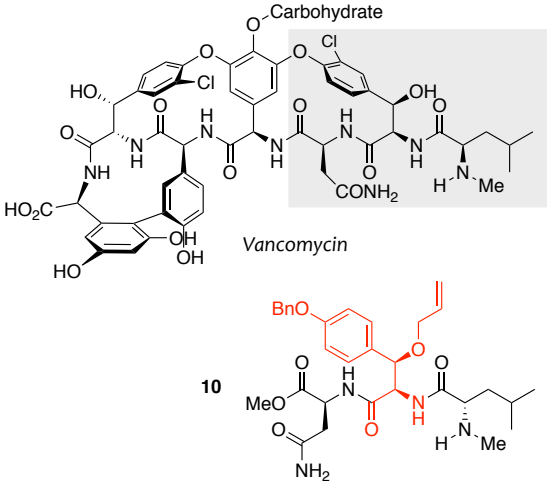
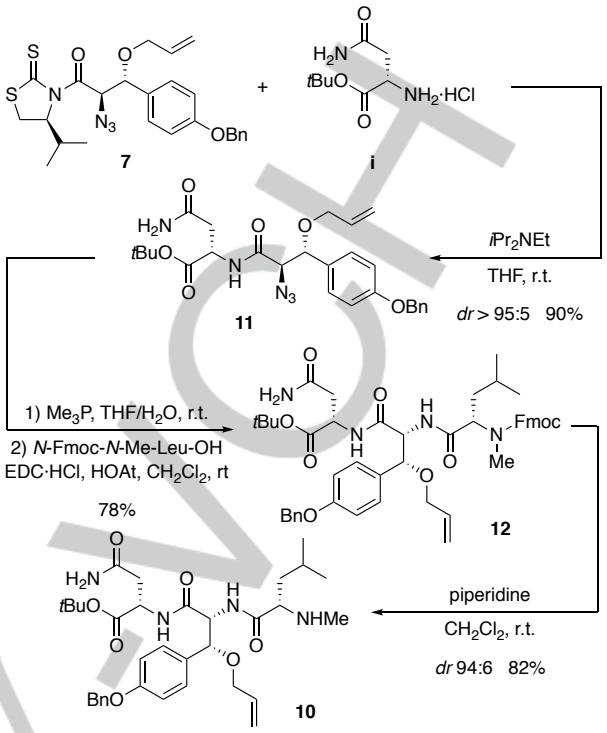


Figure 2. Vancomycin-like tripeptide (**10**) containing a central protected *anti* β–hydroxy tyrosine.

Application of the experimental conditions described in Table 2 to the displacement of the chiral auxiliary from **7** with *tert*-butyl L-asparaginate hydrochloride (**i**) gave dipeptide **11** as a single diastereomer (*dr* > 95:5) in an excellent 90% yield (Scheme 3). Then, reduction of the azido group with Me_3P in THF/H_2O produced the expected amino derivative,[18] which was immediately coupled to *N*-Fmoc-*N*-methyl-L-leucine with EDC·HCl and HOAt to afford fully protected tripeptide **12** with a 78% two-step yield.[19] Finally, removal of the Fmoc protecting group with piperidine permitted us to isolate the desired tripeptide **10** with a 82% yield and a 94:6 diastereomeric ratio as established by HPLC. Therefore, protected tripeptide **10** has been synthesized in a straightforward manner through a four-step sequence from α–azidoacetyl thiazolidinethione **1** with a 43% overall yield.



Scheme 3. Synthesis of a tripeptide containing a central *anti* β-hydroxy tyrosine.

Conclusions

In summary, Lewis acid-mediated additions of (*S*) *N*-azidoacetyl-4-isopropyl-1,3-thiazolidine-2-thione (**1**) to dialkyl acetals of 4-alkoxybenzaldehydes in the presence of 5 mol-% of commercially available and easy to handle $(Me_3P)_2NiCl_2$ produce the corresponding *anti* adducts in high yields and diastereoselectivity. The smooth removal of the chiral auxiliary with a wide range of amino acids provide a variety of dipeptides, whose reduction and further coupling with a third amino acid give access to tripeptidic fragments containing a protected *anti* β-hydroxy tyrosine residue in a highly efficient manner.

Experimental Section

General: Unless otherwise noted, reactions were conducted in oven-dried glassware under inert atmosphere of N_2 with anhydrous solvents. The solvents and reagents were dried and purified when necessary according to standard procedures. Commercially available reagents were used as received. Analytical thin-layer chromatography (TLC) was carried out on Merck silica gel 60 F_{254} plates and analyzed by UV (254 nm) and stained with p-anisaldehyde; column chromatographies were carried under low pressure (flash) conditions and performed on SDS silica gel 60 (35–70 μm). Eluents are indicated in brackets in each case R_f values are approximate. HPLC analyses were conducted on a Shimadzu LC-20 HPLC system, using a C4 reverse phase column at a flow rate of 1 mL min^{-1} and detected at 220 nm. Melting points (Mp) were determined with a Stuart SMP10 apparatus and are uncorrected. Specific

rotations ($[\alpha]_D$) were determined at 20 °C on a Perkin-Elmer 241 MC polarimeter equipped with a sodium lamp (λ 589 nm, D-line). IR spectra (Attenuated Total Reflectance, ATR) were recorded on a Nicolet 6700 FT-IR Thermo Scientific spectrometer and only the more representative frequencies (ν) are reported in cm^{-1}. ^1H NMR (400 MHz) and ^{13}C NMR (100.6 MHz) spectra were recorded at r.t. on a Varian Mercury 400. Chemical shifts (δ) are quoted in ppm and referenced to internal TMS (δ = 0.00 ppm for ^1H NMR) and $CDCl_3$ (δ = 77.0 ppm for ^{13}C NMR). Data are reported as follows: chemical shift (multiplicity, coupling constant(s), number of protons); multiplicity is reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet (and their corresponding combinations); coupling constants (*J*) are quoted in Hz. Where necessary, 2D techniques (NOESY, COSY, HSQC) were also used to assist on structure elucidation. High resolution mass spectra (HRMS) were obtained with an Agilent 1100 spectrometer by the Unitat d'Espectrometria de Masses, Universitat de Barcelona.

General experimental procedure for the addition of 1 to dialkyl acetals: Solid $(Me_3P)_2NiCl_2$ (7.0 mg, 25 μmol, 5 mol-%) was added to a solution of (*S*)-*N*-azidoacetyl-4-isopropyl-1,3-thiazolidine-2-thione (**1**, 122 mg, 0.5 mmol) and the corresponding dialkyl acetal (**2–4**, 0.55 mmol) in CH_2Cl_2 (1.0 mL) under N_2 at r.t. The resulting solution was cooled to –20 °C. Then, TESOTf (170 μL, 0.75 mmol) and 2,6-lutidine (87 μL, 0.75 mmol) were added dropwise after 3 and 7 min respectively and the reaction mixture was stirred at –20 °C for 3 h. The reaction mixture was quenched with sat NH_4Cl (1.2 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), and filtered. They were concentrated and filtered through a pad of silica gel (CH_2Cl_2); the solvent was removed *in vacuo* and the resultant oil was purified by column chromatography to afford the desired product **5–7**.

(*S*) *N*-[(2*R*,3*R*)-2-Azido-3-methoxy-3-(4-methoxyphenyl)propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (5): The reaction was performed from **1** (122 mg, 0.5 mmol) and 4-methoxybenzaldehyde dimethyl acetal (**2**, 94 μL, 0.55 mmol) according to the general procedure to afford an *anti/syn* diastereomeric mixture (dr > 95:5 as established by ^1H NMR analysis of the crude product). Purification of the crude product by column chromatography (CH_2Cl_2/hexanes 80:20) gave 166 mg (0.42 mmol, 84% yield) of **5** as a yellow oil. R_f (CH_2Cl_2/hexanes 80:20) = 0.50. $[\alpha]_D$ = +90.4 (*c* = 1.00, $CHCl_3$). IR (ATR) ν = 2960, 2824, 2095, 1686, 1610, 1360, 1240, 1162 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ = 7.40–7.36 (m, 2H), 6.96–6.93 (m, 2H), 6.50 (d, *J* = 9.0 Hz, 1H), 5.33 (ddd, *J* = 8.4, 5.9, 1.6 Hz, 1H), 4.53 (d, *J* = 9.0 Hz, 1H), 3.83 (s, 3H), 3.42 (dd, *J* = 11.5, 8.4 Hz, 1H), 3.15 (s, 3H), 3.05 (dd, *J* = 11.5, 1.6 Hz, 1H), 2.42–2.31 (m, 1H), 1.10 (d, *J* = 6.8 Hz, 3H), 1.03 (d, *J* = 6.9 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 203.1 (C), 170.5 (C), 160.2 (C), 129.2 (CH), 129.1 (C), 114.1 (CH), 83.8 (CH), 71.8 (CH), 62.5 (CH), 56.5 (CH_3), 55.3 (CH_3), 30.4 (CH_2), 29.8 (CH), 18.9 (CH_3), 17.3 (CH_3) ppm. HRMS (+ESI): *m/z* calcd. for $C_{16}H_{19}N_4O_2S_2$ $[M - OMe]^+$: 363.0944; found: 363.0952.

(*S*) *N*-[(2*R*,3*R*)-2-Azido-3-(4-benzyloxyphenyl)-3-methoxypropanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (6): The reaction was performed from **1** (1.47 g, 6.0 mmol), $(Me_3P)_2NiCl_2$ (84.4 mg, 0.3 mmol, 5 mol-%), and 4-benzyloxybenzaldehyde dimethyl acetal (**3**, 1.70 g, 6.6 mmol) in CH_2Cl_2 (12 mL) under N_2 at r.t. The resulting solution was cooled to –20 °C. Then, TESOTf (2.0 mL, 9.0 mmol) and 2,6-lutidine (1.0 mL, 9.0 mmol) were added dropwise after 3 and 7 min respectively and the reaction mixture was stirred at –20 °C for 3 h. Treatment of the reaction according to the general procedure afforded an *anti/syn* diastereomeric mixture (*dr* > 95:5 as established by ^1H NMR analysis of the crude product). Purification of the crude product by column chromatography (CH_2Cl_2/hexanes 50:50) gave 2.30 g (4.9 mmol, 82% yield) of **6** as a yellow oil. R_f (CH_2Cl_2/Hexanes 50:50) = 0.30. $[\alpha]_D$ = +91.4 (*c* = 2.0, $CHCl_3$). IR (ATR) ν = 2961, 2097, 1689, 1606, 1508, 1359, 1239, 1160 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ = 7.45–7.31 (m, 7H), 7.04–7.00 (m, 2H), 6.50 (d, *J* = 9.0 Hz, 1H), 5.33 (ddd, *J* = 8.0, 6.0, 1.6 Hz, 1H), 5.08 (s, 2H), 4.53 (d, *J* = 9.0 Hz, 1H), 3.54 (dd, *J* = 11.5, 8.0 Hz, 1H), 3.15 (s, 3H), 3.05 (dd, *J* = 11.5, 1.6 Hz, 1H), 2.41–2.32 (m, 1H), 1.10 (d, *J* = 6.8 Hz, 3H), 1.03 (d, *J* = 6.9 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 203.1 (C), 170.5 (C), 159.4 (C), 136.8 (C), 129.4 (C), 129.3 (CH), 128.6 (CH), 128.0 (CH), 127.5 (CH), 115.0 (CH), 83.8 (CH), 71.8 (CH), 70.0 (CH_2), 62.5 (CH), 56.6 (CH_3), 30.4 (CH), 29.8 (CH_2), 18.9 (CH_3), 17.3 (CH_3) ppm. HRMS (+ESI): *m/z* calcd. for $C_{22}H_{23}N_4O_2S_2$ $[M - OMe]^+$: 439.1257; found: 439.1253.

(*S*) *N*-[(2*R*,3*R*)-3-Allyloxy-2-azido-3-(4-benzyloxyphenyl)propanoyl]-4-isopropyl-1,3-thiazoli-dine-2-thione (7): The reaction was performed from **1** (244 mg, 1.0 mmol), $(Me_3P)_2NiCl_2$ (14.1 mg, 50 μmol, 5 mol-%), and 4-benzyloxybenzaldehyde diallyl acetal (**4**, 341 mg, 1.1 mmol) in CH_2Cl_2 (2 mL) under N_2 at r.t. The resulting solution was cooled to –20 °C. Then, TESOTf (340 μL, 1.5 mmol) and 2,6-lutidine (177 μL, 1.5 mmol) were added dropwise after 3 and 7 min respectively and the reaction mixture was stirred at –20 °C for 3 h. Treatment of the reaction according to the general procedure afforded an *anti/syn* diastereomeric mixture (*dr* > 95:5 as established by ^1H NMR analysis of the crude product). Purification of the crude product by column chromatography (from CH_2Cl_2/hexanes 60:40 to 70:30) gave 337 mg (0.76 mmol, 76% yield) of **7** as a yellow oil. R_f (CH_2Cl_2/Hexanes 60:40) = 0.30. $[\alpha]_D$ = +123.0 (*c* = 1.0, $CHCl_3$). IR (ATR) ν = 2962, 2872, 2105, 1692, 1608, 1509, 1362, 1242, 1163 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ = 7.45–7.32 (m, 7H), 7.03–7.00 (m, 2H), 6.49 (d, *J* = 9.0 Hz, 1H), 5.80–5.70 (m, 1H), 5.32 (ddd, *J* = 8.3, 6.0, 1.3 Hz, 1H), 5.18 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.11–5.08 (m, 1H), 5.08 (s, 2H), 4.74 (d, *J* = 9.0 Hz, 1H), 3.88 (ddt, *J* = 12.7, 4.9, 1.7 Hz, 1H), 3.74 (ddt, *J* = 12.7, 6.2, 1.7 Hz, 1H), 3.54 (dd, *J* = 11.5, 8.3 Hz, 1H), 3.04 (dd, *J* = 11.5, 1.3 Hz, 1H), 2.41–2.31 (m, 1H), 1.08 (d, *J* = 6.8 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 203.0 (C), 170.1 (C), 159.4 (C), 136.8 (C), 134.0 (CH), 129.6 (C), 129.3 (CH), 128.6 (CH), 128.0 (CH), 127.5 (CH), 117.1 (CH_2), 115.0 (CH), 81.0 (CH), 71.8 (CH), 70.0 (CH_2), 69.5 (CH_2), 62.4 (CH), 30.5 (CH), 29.8 (CH_2), 19.1 (CH_3), 17.5 (CH_3) ppm. HRMS (+ESI): *m/z* calcd. for $C_{22}H_{23}N_4O_2S_2$ $[M - OAllyl]^+$: 439.1257; found: 439.1261.

General experimental procedure for the removal of the chiral auxiliary of 5 with amino acids containing primary amino groups: Distilled *i*Pr_2NEt (2 equiv) was added to a mixture of the corresponding hydrochloride amino ester **a–e** (1.1 equiv) and **5** (1 equiv) in THF (0.15 M) at 0 °C under N_2. The reaction was stirred for 30 min at 0 °C and 4 h at r.t. The volatiles were evaporated. The crude mixture was diluted in CH_2Cl_2 (10 mL) and washed with 1 M NaOH (3 × 15 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The resulting mixture was purified by column chromatography to afford the corresponding product.

Displacement with methyl β-alaninate hydrochloride, 8a: The reaction was carried out according to the General Procedure from **5** (50 mg, 127 μmol), **a** (20 mg, 143 μmol), and *i*Pr_2NEt (44 μL, 254 μmol). The purification of the crude mixture by column chromatography (from Hexanes/EtOAc 80:20 to 60:40) afforded 41 mg (121 μmol, *dr* > 95:5, 96% yield) of methyl *N*-[(2*R*,3*R*)-2-azido-3-methoxy-3-(4-methoxyphenyl)propanoyl]-β-alaninate (**8a**) as a yellowish oil. R_f (Hexanes/EtOAc 80:20) = 0.10. $[\alpha]_D$ = –188.1 (*c* = 1.00, $CHCl_3$). IR (ATR) ν = 3330, 2950, 2106, 1732, 1663, 1511, 1246, 1172 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ = 7.24–7.22 (m, 2H), 6.87–6.84 (m, 2H), 6.57 (t (br), *J* = 5.5 Hz, 1H), 4.79 (d, *J* = 4.1 Hz, 1H), 4.32 (d, *J* = 4.1 Hz, 1H), 3.80 (s, 3H), 3.61 (s, 3H), 3.47–3.39 (m, 1H), 3.30 (s, 3H), 3.27–3.21 (m, 1H), 2.37 (ddd, *J* = 17.4, 6.3, 4.6 Hz, 1H), 2.19 (ddd, *J* = 17.4, 8.5, 4.9 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 172.3 (C), 166.6 (C), 159.7 (C),

129.0 (CH), 127.6 (C), 113.5 (CH), 83.6 (CH), 67.5 (CH), 56.8 (CH_3), 55.1 (CH_3), 51.7 (CH_3), 34.3 (CH_2), 33.4 (CH_2) ppm. HRMS (+ESI): *m/z* calcd. for $C_{15}H_{20}N_4NaO_5$ [M + Na]$^+$: 359.1326; found: 359.1323.

Displacement with methyl L-alaninate hydrochloride, 8b: The reaction was carried out according to the General Procedure from **5** (50 mg, 127 µmol), **b** (20 mg, 143 µmol), and *i*Pr$_2$NEt (44 µL, 254 µmol). The purification of the crude mixture by column chromatography (from Hexanes/EtOAc 80:20 to 60:40) afforded 41 mg (121 µmol, *dr* > 95:5, 96% yield) of methyl *N*-[(2*R*,3*R*)-2-azido-3-methoxy-3-(4-methoxyphenyl)propanoyl]-L-alaninate (**8b**) as a yellowish oil. R_f (Hexanes/EtOAc 80:20) = 0.10. $[\alpha]_D$ = –149.1 (*c* = 1.00, $CHCl_3$). IR (ATR) ν = 3309, 2937, 2104, 1740, 1661 1511, 1247, 1096 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.26–7.23 (m, 2H), 6.89–6.85 (m, 2H), 6.62 (d (br), *J* = 7.3 Hz, 1H), 4.75 (d, *J* = 4.5 Hz, 1H), 4.43 (quintet, *J* = 7.3 Hz, 1H), 4.37 (d, *J* = 4.5 Hz, 1H), 3.81 (s, 3H), 3.65 (s, 3H), 3.31 (s, 3H), 1.35 (d, *J* = 7.3 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 172.4 (C), 166.5 (C), 159.9 (C), 129.0 (CH), 127.7 (C), 113.8 (CH), 83.6 (CH), 67.6 (CH), 57.0 (CH_3), 55.4 (CH_3), 52.5 (CH_3), 48.1 (CH), 18.5 (CH_3) ppm. HRMS (+ESI): *m/z* calcd. for $C_{15}H_{20}N_4NaO_5$ [M + Na]$^+$: 359.1326; found: 359.1315.

Displacement with methyl L-leucinate hydrochloride, 8c: The reaction was carried out according to the General Procedure from **5** (57 mg, 144 µmol), **c** (28 mg, 154 µmol) and *i*Pr$_2$NEt (49 µL, 280 µmol). The purification of the crude mixture by column chromatography (from hexanes/EtOAc 85:15 to 50:50) afforded 51 mg (130 µmol, *dr* > 95:5, 96% yield) of methyl (*S*)-*N*-[(2*R*,3*R*)-2-azido-3-methoxy-3-(4-methoxyphenyl)propanoyl]-L-leucinate (**8c**) as a yellowish oil. R_f (hexanes/EtOAc 85:15) = 0.20. $[\alpha]_D$ = –97.8 (*c* = 1.0, $CHCl_3$). IR (ATR) ν = 3308, 2954, 2104, 1743, 1660 1511, 1246, 1173 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.26–7.22 (m, 2H), 6.89–6.85 (m, 2H), 6.42 (d, *J* = 8.4 Hz, 1H), 4.73 (d, *J* = 4.7 Hz, 1H), 4.51 (td, *J* = 8.7, 5.1 Hz, 1H), 4.36 (d, *J* = 4.7 Hz, 1H), 3.81 (s, 3H), 3.61 (s, 3H), 3.30 (s, 3H), 1.62–1.45 (m, 3H), 0.92 (d, *J* = 6.1 Hz, 3H), 0.91 (d, *J* = 6.2 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ =172.2 (C), 166.7 (C), 159.9 (C), 129.0 (CH), 127.9 (C), 113.8 (C, CH), 83.6 (CH), 67.6 (CH), 57.0 (CH_3), 55.3 (CH_3), 52.3 (CH_3), 50.7 (CH), 41.7 (CH_2), 24.8 (CH), 22.9 (CH_3), 22.0 (CH_3) ppm. HRMS (+ESI): *m/z* calcd. for $C_{18}H_{27}N_4O_5$ [M + H]$^+$: 379.1976; found: 379.1973.

Displacement with methyl L-phenylalalinate hydrochloride, 8d: The reaction was carried out according to the General Procedure from **5** (50 mg, 127 µmol), **d** (30 mg, 139 µmol) and *i*Pr$_2$NEt (44 µL, 254 µmol). The purification of the crude mixture by column chromatography (from Hexanes/EtOAc 80:20 to 60:40) afforded 45 mg (109 µmol, *dr* > 95:5, 87% yield) of methyl *N*-[(2*R*,3*R*)-2-azido-3-methoxy-3-(4-methoxyphenyl)propanoyl]-L-phenylalaninate (**8d**) as a yellowish solid. Mp = 103–105 °C. R_f (Hexanes/EtOAc 80:20 = 0.10). $[\alpha]_D$ = –85.8 (*c* = 1.00, $CHCl_3$). IR (ATR) ν = 3337, 2936, 2102, 1736, 1648, 1509, 1249, 1100 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.30–7.20 (m, 5H), 7.09–7.05 (m, 2H), 6.86–6.84 (m, 2H), 6.58 (d, *J* = 7.9 Hz, 1H), 4.73 (dt, *J* = 7.9, 6.0 Hz, 1H), 4.67 (d, *J* = 4.9 Hz, 1H), 4.30 (d, *J* = 4.9 Hz, 1H), 3.79 (s, 3H), 3.60 (s, 3H), 3.24 (s, 3H), 3.10 (dd, *J* = 13.9, 6.0 Hz, 1H), 3.01 (dd, *J* = 13.9, 6.0 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 170.8 (C), 166.6 (C), 159.7 (C), 135.6 (C), 129.2 (CH), 128.8 (CH), 128.5 (CH), 127.7 (C), 127.1 (CH), 113.6 (CH), 83.2 (CH), 67.4 (CH), 56.8 (CH_3), 55.2 (CH_3), 53.1 (CH), 52.2 (CH_3), 37.9 (CH_2) ppm. HRMS (+ESI): *m/z* calcd. for $C_{21}H_{24}N_4NaO_5$ [M + Na]$^+$: 435.1639; found: 435.1637.

Displacement with methyl valinate hydrochloride, 8e: The reaction was carried out according to the General Procedure from **5** (59 mg, 150 µmol), **e** (28 mg, 167 µmol) and *i*Pr$_2$NEt (52 µL, 0.3 mmol). The purification of the crude mixture by column chromatography (from Hexanes/EtOAc 85:15 to 70:30) afforded 47 mg (130 µmol, *dr* > 95:5, 86% yield) of methyl *N*-[(2*R*,3*R*)-2-azido-3-methoxy-3-(4-methoxyphenyl)propanoyl]-L-valinate (**8e**) as a yellowish oil. R_f (Hexanes/EtOAc 85:15) = 0.15. $[\alpha]_D$ = –130.4 (*c* = 1.00, $CHCl_3$). IR (ATR) ν = 3325, 2960, 2102, 1703, 1663, 1511, 1208, 1098 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.26–7.19 (m, 2H), 6.89–6.86 (m, 2H), 6.51 (d, *J* = 8.8 Hz, 1H), 4.70 (d, *J* = 5.0 Hz, 1H), 4.40 (dd, *J* = 8.8, 5.3 Hz, 1H), 4.36 (d, *J* = 5.0 Hz, 1H), 3.81 (s, 3H), 3.62 (s, 3H), 3.30 (s, 3H), 2.12–2.04 (m, 1H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.86 (d, *J* = 6.9 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 171.3 (C), 167.0 (C), 159.9 (C), 128.9 (CH), 127.9 (C), 113.8 (CH), 83.6 (CH), 67.6 (CH), 57.2 (CH), 57.0 (CH_3), 55.3 (CH_3), 52.1 (CH_3), 31.6 (CH), 19.0 (CH_3), 17.9 (CH_3) ppm. HRMS (+ESI): *m/z* calcd. for $C_{17}H_{25}N_4O_5$ [M + H]$^+$: 365.1819, found: 365.1820.

Removal of the chiral auxiliary with amino acids containing secondary amino groups.

Reaction of 1 with methyl L-prolinate hydrochloride. Synthesis of 9f: A mixture of **1** (122 mg, 0.5 mmol), methyl L-prolinate hydrochloride (91 mg, 0.55 mmol), and *i*Pr$_2$NEt (174 µL, 1.0 mmol) in THF (2.5 mL) was stirred for 30 min at 0 °C and 4 h at r.t. under N_2.The volatiles were evaporated. The crude mixture was diluted in CH_2Cl_2 (20 mL) and washed with 1 M NaOH (3 × 30 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The resulting mixture was purified by column chromatography (from CH_2Cl_2 to CH_2Cl_2/EtOAc 90:10) to afford 79 mg (0.37 mmol, 75% yield) of methyl *N*-(2-azidoacetyl)-L-prolinate (**9f**) as a 5:1 mixture of rotamers. Colorless oil. R_f (CH_2Cl_2) = 0.10. $[\alpha]_D$ = –114.2 (*c* = 1.00, $CHCl_3$). IR (ATR) ν = 2954, 2881, 2100, 1737, 1651, 1436, 1170 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 4.56 (dd, *J* = 8.6, 3.7 Hz, 1H), 3.90 (s, 2H), 3.75 (s, 3H), 3.61–3.57 (m, 1H), 3.48–3.42 (m, 1H), 2.28–2.00 (m, 4H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 172.2 (C), 166.1 (C), 59.0 (CH), 52.4 (CH_3), 50.9 (CH_2), 46.3 (CH_2), 29.0 (CH_2), 24.8 (CH_2) ppm. HRMS (+ESI): *m/z* calcd. for $C_8H_{13}N_4O_3$ [M + H]$^+$: 213.0979, found: 213.0982.

Reaction of 1 with methyl L-pipecolate hydrochloride. Synthesis of 9g: A mixture of **1** (122 mg, 0.5 mmol), methyl L-pipecolate hydrochloride (99 mg, 0.55 mmol), and *i*Pr$_2$NEt (174 µL, 1.0 mmol) in THF (2.5 mL) was stirred for 30 min at 0 °C and 4 h at r.t. under N_2. The volatiles were evaporated. The crude mixture was diluted in CH_2Cl_2 (20 mL) and washed with 1 M NaOH (3 × 30 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The resulting mixture was purified by column chromatography (from CH_2Cl_2 to CH_2Cl_2/EtOAc 90:10) to afford 51 mg (0.21 mmol, 42% yield) of starting material **1** and 45 mg (0.20 mmol, 40% yield) of methyl *N*-(2-azidoacetyl)-L-pipecolate (**9g**) as a 5:1 mixture of rotamers. Colorless oil. R_f (CH_2Cl_2) = 0.10. $[\alpha]_D$ = –77.7 (*c* = 1.00, $CHCl_3$). IR (ATR) ν = 2946, 2102, 1735, 1651, 1445, 1204, 1020 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 5.34 (d, *J* = 5.6 Hz, 1H), 3.99 (s, 2H), 3.75 (s, 3H), 3.56–3.52 (m, 1H), 3.29 (td, *J* = 13.0, 3.0 Hz, 1H), 3.33–3.27 (m, 1H), 1.77–1.64 (m, 3H), 1.50–1.32 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 171.4 (C), 167.4 (C), 52.5 (CH_3), 52.4 (CH), 50.9 (CH_2), 43.1 (CH_2), 26.7 (CH_2), 25.2 (CH_2), 20.9 (CH_2) ppm. HRMS (+ESI): *m/z* calcd. for $C_9H_{15}N_4O_3$ [M+H]$^+$: 227.1139; found: 227.1146.

Reaction of 5 with methyl L-prolinate. Synthesis of 8f: A solution of **5** (20 mg, 51 µmol) and methyl L-prolinate (14.4 mg, 112 µmol) in CH_2Cl_2 (0.3 mL) was stirred a few minutes at 0 °C under N_2 and 4 h at r.t. The volatiles were evaporated. The crude mixture was diluted in CH_2Cl_2 (5 mL) and washed with 1 M NaOH (3 × 10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The resulting mixture was purified by column chromatography (Hexanes/EtOAc 80:20) to afford 13 mg (36 µmol, *dr* > 95:5, 72% yield) of methyl *N*-[(2*R*,3*R*)-2-azido-3-methoxy-3-(4-methoxyphenyl)-propanoyl]-L-prolinate (**8f**) as a yellowish oil. R_f (Hexanes/EtOAc 80:20) = 0.10. $[\alpha]_D$ = –45.0 (*c* = 1.00, $CHCl_3$). IR (ATR) ν = 2952, 2100, 1741, 1650, 1511, 1433, 1247, 1172 cm^{-1}. ^{1}H

NMR ($CDCl_3$, 400 MHz) δ = 7.34–7.30 (m, 2H), 6.96–6.92 (m, 2H), 4.59 (dd, *J* = 8.4, 4.0 Hz, 1H), 4.54 (d, *J* = 9.3 Hz, 1H), 3.83 (d, *J* = 9.3 Hz, 1H), 3.83 (s, 3H), 3.75 (s, 3H), 3.72–3.68 (m, 2H), 3.18 (s, 3H), 2.26–2.20 (m, 1H), 2.13–1.97 (m, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 172.3 (C), 167.5 (C), 160.2 (C), 129.7 (C), 128.8 (CH), 114.3 (CH), 82.5 (CH), 63.8 (CH), 59.3 (CH), 57.0 (CH_3), 55.4 (CH_3), 52.5 (CH_3), 47.2 (CH_2), 29.3 (CH_2), 24.9 (CH_2) ppm. HRMS (+ESI): *m/z* calcd. for $C_{17}H_{23}N_4O_5$ $[M+H]^+$: 363.1663, found: 363.1664.

Synthesis of tripeptide 10.

***tert*-Butyl *N*-[(2*R*,3*R*)-3-allyloxy-2-azido-3-(4-benzyloxyphenyl)propanoyl]-L-asparaginate (11):** Neat *i*Pr_2NEt (75 µL, 430 µmol) was added to a solution of *tert*-butyl L-asparaginate hydrochloride (53 mg, 237 µmol) and **7** (107 mg, 215 µmol) in THF (1.5 mL) at 0 °C under N_2 and the resulting mixture was stirred for 4 h at r.t. The volatiles were evaporated. The residue was diluted in CH_2Cl_2 (5 mL) and washed with 1 M NaOH (3 × 10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification of the crude mixture by column chromatography (CH_2Cl_2/EtOAc 90:10 and then CH_2Cl_2/MeOH 95:5) afforded 102 mg (195 µmol, *dr* > 95:5, 90% yield) of *tert*-butyl *N*-[(2*R*,3*R*)-3-allyloxy-2-azido-3-(4-benzyloxyphenyl)propanoyl]-L-asparaginate (**11**) as a yellow solid. Mp = 53–55 °C. R_f (CH_2Cl_2/MeOH 95:5) = 0.30. $[\alpha]_D$ = –81.6 (c 1.00, $CHCl_3$). IR (ATR) ν = 3343 (bs), 2978, 2829, 2107, 1731, 1688, 1510, 1243, 1156 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ = 7.44–7.31 (m, 5H), 7.29–7.25 (m, 2H), 7.21 (bd, *J* = 7.5 Hz, 1H), 6.97–6.93 (m, 2H), 5.92–5.82 (m, 1H), 5.71 (bs, 1H), 5.45 (bs, 1H), 5.25 (dq, *J* = 17.3, 1.7 Hz, 1H), 5.16 (dq, *J* = 10.5, 1.7 Hz, 1H), 5.04 (s, 2H), 4.88 (d, *J* = 5.3 Hz, 1H), 4.49 (dt, *J* = 7.5, 4.9 Hz, 1H), 4.30 (d, *J* = 5.3 Hz, 1H), 3.98 (ddt, *J* = 12.9, 4.7, 1.7 Hz, 1H), 3.84 (ddt, *J* = 12.9, 6.9, 1.7 Hz, 1H), 2.75 (d, *J* = 4.9 Hz, 2H), 1.40 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 171.6 (C), 168.9 (C), 167.0 (C), 159.1 (C), 136.8 (C), 134.0 (CH), 129.0 (CH), 128.6 (CH), 128.4 (C), 128.0 (CH), 127.5 (CH), 117.0 (CH_2), 114.6 (CH), 82.6 (C), 80.8 (CH), 70.0 (CH_2), 69.5 (CH_2), 67.4 (CH), 49.7 (CH), 37.4 (CH_2), 27.8 (CH_3) ppm. HRMS (+ESI): *m/z* calcd. for $C_{27}H_{33}N_5NaO_6$ $[M + Na]^+$: 546.2323; found: 546.2332.

***N*-Fmoc-*N*-Me-Leu-β-OAllyl-Tyr(Bn)-Asp(O*t*-Bu) (12)**

Reduction of **11**: A 1 M solution of Me_3P in THF (367 µL, 367 µmol) was added to a solution of **11** (175 mg, 334 µmol) in 90:10 THF/H_2O (2.6 mL) under N_2 at r.t. and the resulting mixture was stirred fo 2 h. It was diluted in EtOAc (10 mL) and washed with H_2O (3 × 15 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to afford 154 mg (309 µmol, 93% yield) of the corresponding amino ester, which was used in the next step without further purification. Colorless solid. Mp = 51–53 °C. $[\alpha]_D$ = +1.4 (c 1.00, $CHCl_3$). IR (ATR) ν = 3316 (bs), 2976, 2928, 1727, 1661, 1508, 1220, 1153 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ = 7.79 (d, *J* = 7.5 Hz, 1H), 7.44–7.31 (m, 5H), 7.25–7.22 (m, 2H), 6.97–6.93 (m, 2H), 6.01 (bs, 1H), 5.93–5.83 (m, 1H), 5.48 (bs, 1H), 5.22 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.15 (dq, *J* = 10.4, 1.7 Hz, 1H), 5.04 (s, 2H), 4.74 (d, *J* = 5.8 Hz, 1H), 4.59 (dt, *J* = 7.5, 5.1 Hz, 1H), 3.69 (d, *J* = 5.8 Hz, 1H), 3.98 (ddt, *J* = 12.7, 5.1, 1.7 Hz, 1H), 3.84 (ddt, *J* = 12.7, 6.1, 1.7 Hz, 1H), 2.77 (d, *J* = 5.1 Hz, 2H), 1.42 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 172.5 (C), 171.8 (C), 169.5 (C), 158.8 (C), 136.9 (C), 134.4 (CH), 129.4 (C), 128.9 (CH), 128.6 (CH), 128.0 (CH), 127.5 (CH), 117.1 (CH_2), 114.7 (CH), 82.4 (C), 81.3 (CH), 70.0 (CH_2), 69.6 (CH_2), 59.9 (CH), 49.5 (CH), 37.9 (CH_2), 27.8 (CH_3) ppm.

Coupling with *N*-Fmoc-*N*-methyl-L-leucine: A solution of *N*-Fmoc-*N*-methyl-L-leucine (55 mg, 150 µmol) in CH_2Cl_2 (0.5 mL) was added via *cannula* to a solution of the abovementioned amino ester (51 mg, 100 µmol), HOAt (45 mg, 330 µmol), and EDC·HCl (58 mg, 300 µmol) in CH_2Cl_2 (0.5 mL) under N_2 at 0 °C. The resultant mixture was stirred for 1 h at 0 °C and 15 h at r.t. The reaction was quenched with sat $NaHCO_3$ (1 mL), vigorously stirred for 15 min, and extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered, and evaporated. Purification of the crude mixture by column chromatography (Hexanes/EtOAc 30:70, then CH_2Cl_2/MeOH 95:5) afforded 71 mg (84 µmol, 84% yield; 78% overall yield) of **12** as a 5:1 mixture of rotamers. Colorless solid. Mp = 75–77 °C. R_f (CH_2Cl_2/MeOH 95:5) = 0.32. $[\alpha]_D$ = –32.0 (c 1.00, $CHCl_3$). IR (ATR) ν = 3303, 2928, 1735, 1658 (bs), 1610, 1510, 1154 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ = 7.77–7.75 (m, 2H), 7.60–7.57 (m, 2H), 7.41–7.21 (m, 13H), 6.93–6.91 (m, 2H), 5.98–5.80 (m, 2H), 5.41 (bs, 1H), 5.21–5.16 (m, 1H), 5.14–5.11 (m, 1H), 4.96 (s, 2H), 4.71–4.52 (m, 4H), 4.45–4.36 (m, 2H), 4.30–4.22 (m, 1H), 3.95–3.87 (m, 1H), 3.81–3.73 (m, 1H), 2.78 (s, 3H), 2.76–2.72 (m, 2H), 1.49–1.37 (m, 1H), 1.42 (s, 9H), 1.31–1.22 (m, 2H), 0.87–0.83 (m, 6H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 171.6 (C), 170.6 (2 × C), 169.2 (C), 159.0 (C), 157.1 (C), 143.8 (C), 141.3 (C), 136.8 (C), 134.0 (CH), 129.2 (C), 128.7 (CH), 128.5 (CH), 128.0 (CH), 127.7 (CH), 127.5 (CH), 127.1 (CH), 125.0 (CH), 120.0 (CH), 117.6 (CH_2), 114.7 (CH), 82.5 (C), 80.1 (CH), 69.9 (CH_2), 69.8 (CH_2), 67.9 (CH_2), 57.4 (CH), 57.2 (CH), 49.9 (CH), 47.2 (CH), 37.7 (CH_2), 36.6 (CH_2), 30.2 (CH_3), 27.8 (CH_3), 24.6 (CH), 23.0 (CH_3), 21.9 (CH_3) ppm. HRMS (+ESI): *m/z* calcd. for $C_{46}H_{53}N_4O_8$ $[M – OAllyl]^+$: 789.3858; found: 789.3853.

H-*N*-Me-Leu-β-OAllyl-Tyr(Bn)-Asp(O*t*-Bu) (10): A 10-% (v/v) solution of piperidine in CH_2Cl_2 (103 µL,104 µmol) was added to a solution of **12** (30 mg, 35 µmol) in CH_2Cl_2 (0.4 mL) at 0 °C under N_2 and the resulting mixture was stirred for one day at r.t. The volatiles were evaporated. Purification of the residue by column chromatography (from CH_2Cl_2/MeOH 95:5 to 90:10) afforded 19 mg (30 µmol, 82% yield) of a 94:6 diastereomeric mixture (HPLC analysis) of tripeptide **10** as a colorless solid. Mp **=** 180–182 °C. R_f (CH_2Cl_2/MeOH 95:5) = 0.13. HPLC (C4 reverse phase column, from 30% to 40% of CH_3CN in H_2O, 1 mL/min, 220 nm), t_R = 7.02 min. $[\alpha]_D$ = –16.1 (*c* 1.00, $CHCl_3$). IR (ATR) ν = 3286, 2924, 2853, 1733, 1656 (bs), 1510, 1242, 1157 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ = 7.62 (bs, 1H), 7.43–7.22 (m, 8H), 6.96–6.93 (m, 2H), 6.06 (bs, 1H), 5.90–5.81 (m, 1H), 5.51 (bs, 2H), 5.22 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.15 (dq, *J* = 10.4, 1.6 Hz, 1H), 5.04 (s, 2H), 4.75–4.71 (m, 2H), 4.67–4.62 (m, 1H), 3.93 (dd, *J* = 12.8, 5.1 Hz, 1H), 3.81 (ddt, *J* = 12.8, 6.5 Hz, 1H), 2.88–2.84 (m, 1H), 2.77 (d, *J* = 4.5 Hz, 2H), 2.12 (s, 3H), 1.49–1.37 (m, 1H), 1.45 (s, 9H), 1.31–1.22 (m, 2H), 0.86 (d, *J* = 9.2 Hz, 3H), 0.84 (d, *J* = 9.1 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 171.7 (C), 169.6 (2 × C), 169.2 (C), 159.0 (C), 136.8 (C), 134.2 (CH), 129.4 (C), 128.9 (CH), 128.6 (CH), 128.0 (CH), 127.5 (CH), 117.4 (CH_2), 114.8 (CH), 82.6 (C), 79.9 (CH), 70.0 (CH_2), 69.7 (CH_2), 63.1 (CH), 57.1 (CH), 49.8 (CH), 42.4 (CH_2), 37.9 (CH_2), 35.0 (CH_3), 27.9 (CH_3), 25.0 (CH), 23.0 (CH_3), 21.9 (CH_3) ppm. HRMS (+ESI): *m/z* calcd. for $C_{34}H_{49}N_4O_7$ $[M + H]^+$: 625.3596; found: 625.3591.

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Layout 2:

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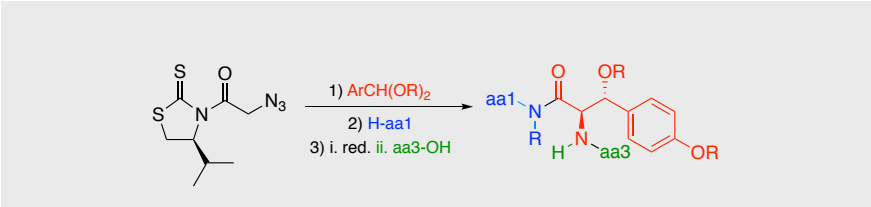

Stereoselective Synthesis

Javier Fernández-Valparis, Pedro Romea, and Fèlix Urpí**

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Stereoselective Synthesis of Protected Peptides Containing an *anti* β-Hydroxy Tyrosine

Direct, stereoselective, and catalyzed addition of a chiral *N*-azidoacetyl thiazolidinethione to dialkyl acetals followed by removal of the scaffold with an amino ester, reduction of the azido group and coupling with an amino acid yields peptide fragments containing a protected β-hydroxy tyrosine