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ORIGINAL ARTICLE

Synthesis of 4-hydroxy-β^3-homoprolines and their insertion in $\alpha/\beta/\alpha$-tripeptides

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Abstract The stereoselective syntheses of 2-cyclopropyl- and (2*S*)-2-hydroxymethyl-(3*R*,4*S*)-4-hydroxy-β^3-homoproline are described. The reported amino acids were constructed through 1,3-dipolar cycloaddition of strained alkylidenecyclopropanes with enantiopure pyrroline *N*-oxides derived from malic acid followed by thermal rearrangement of the adducts in the presence of trifluoroacetic acid. The two-step sequence afforded the homoprolines suitably protected to be directly used as building blocks in peptidomimetic synthesis as proved by the synthesis of the two model mixed $\alpha/\beta/\alpha$ tripeptides Phe-β^3-HPro-Val.

Keywords Cycloaddition · Rearrangement · Peptidomimetics · Heterocycles · Small ring systems

Introduction

β-Amino acids are a class of interesting compounds frequently found in biologically active products (for example, β-alanine, β-tyrosine, and α-hydroxy-β-phenylalanine are components of the vitamin pantothenic acid, the antibiotic edenine A, and the anticancer Taxol®, respectively) and commonly used as synthetic intermediates and building blocks of peptidomimetics in general and β-peptides in particular (for a selection of recent reviews on β-amino acids, see: Szakonyi and Fülöp 2011; Weiner et al. 2010; Kiss and Fülöp 2010; Seebach et al. 2009; Horne and Gellman 2008; Liljeblad and Kanerva 2006; Kuhl et al. 2005; Steer et al. 2002; Juaristi and López-Ruiz 1999). More recently, the use of β-amino acids as organocatalysts was also reported (Terakado et al. 2005; Mitsumori et al. 2006; Limbach 2006; Davies et al. 2007; Gruttadauria et al. 2008; Tsandi et al. 2009; Hiraga et al. 2011; Yang and Wong 2011).

β^3-Homoproline (pyrrolidine-2-acetic acid, β^3-HPro, **1**) (Fig. 1) is of particular interest. For example, this β-amino acid has been used in place of proline to produce biological active mimics that are not degraded by peptidases (Balá-spiri et al. 1975; Ondetti and Engel 1975; Szirtes et al. 1986; Aguilar et al. 2007; Katarzyńska et al. 2008). In addition, a variety of derivatives of both (3*S*)- and (3*R*)-β^3-HPro show biological and pharmacological activities (Deutsch et al. 2001; Davies et al. 2004; Fülep et al. 2006; Zhu et al. 2009; Andries et al. 2011) and were used as synthetic intermediates of various aza-heterocycles (Luly and Rapoport 1983; Rabiczko et al. 2002; Ranatunga et al. 2010). Finally, the conformational behavior of β^3-HPro (Góbi et al. 2010) and the secondary structure of its oligomers were investigated (Abele et al. 1999). Thus, the synthesis and study of these β-amino acids in enantiopure form is an important area within organic chemistry, and new approaches to C-2-substituted derivatives of **1**, unavailable by simple homologation of proline, are highly desirable (for some examples of optically active 2-substituted β^3-homoprolines, see: Yi et al. 2003; Davies et al. 2004; Saavedra et al. 2009; Ranatunga et al. 2010; Benz et al. 2011). We have previously shown that adducts of pyrroline *N*-oxides **3** with methylenecyclopropane (MCP) and bicyclopropylidene (BCP) such as **4** and **5** undergo a thermal rearrangement with fragmentation in the presence of trifluoroacetic acid (TFA) to *N*-trifluoroacetyl β^3-homoprolines **6** and **7**, respectively (Fig. 2) (Cordero et al. 2004a, 2009).

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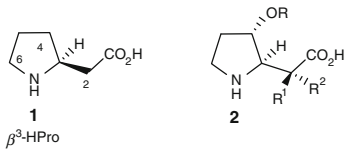


Fig. 1 Structures of β^3-homoproline (**1**) and 4-hydroxy derivatives **2**

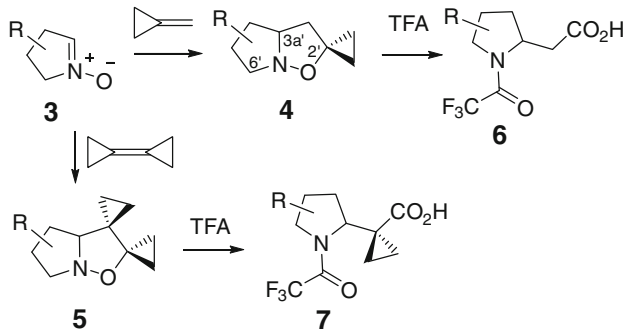


Fig. 2 Synthesis of *N*-trifluoroacetyl β^3-homoprolines by 1,3-DC/ATR

Here, we present the application of this two-step sequence 1,3-dipolar cycloaddition (1,3-DC)/acidic thermal rearrangement (ATR) to the synthesis of 4-hydroxy-β^3-homoprolines **2** (Fig. 1) having a cyclopropane ring (R^1–R^2 = CH_2–CH_2) and a 2-hydroxyethyl chain on C-2 (R^1 = H, R^2 = CH_2-CH_2OH) and their incorporation in a $\alpha/\beta/\alpha$ tripeptide.

Results and discussion

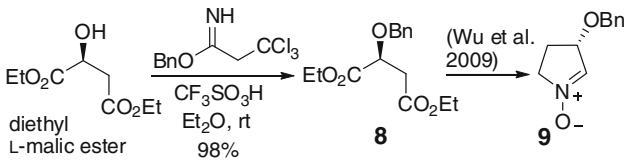
The use of an enantiopure 4-hydroxy pyrroline *N*-oxide as building block in the synthesis of β^3-homoprolines offers valuable opportunities. The presence of a bulky group on nitrone C-4 such as O*t*Bu group can force the dipolarophile to add only on the less hindered nitrone diastereoface (Zorn et al. 1999). As a consequence, complete control of configuration of the isoxazolidine C-3a′ and, therefore, of the homoproline C-3 stereocenter could be achieved. Moreover, the presence of the hydroxy group can confer important properties to the final homoproline. In this regard, we just recall the most common posttranslational modification of proline (Pro) into 4-hydroxyproline (HYP) that is an essential stabilizer of collagen structure (Persikov et al. 2000; Berisio et al. 2002; Schumacher et al. 2006; Krane 2008; Gorres and Raines 2010).

Protected 4-hydroxy pyrroline *N*-oxides can be conveniently prepared in enantiopure form from malic acid, a common chiral pool compound available in both the enantiomeric forms (Cicchi et al. 1995; Goti et al. 1997, 1999, 2000; Ohtake et al. 1999; Cordero et al. 2002; Merino et al. 2003; Wu et al. 2009; Delso et al. 2010). The *O-tert*-butyl- and *O*-benzyl-protected nitrones used in the synthesis of homoprolines **2** were prepared following previously reported procedures (Cicchi et al. 1995, 2001; Wu et al. 2009) except for the benzylation step. In particular, treatment of diethyl malic ester with benzyl trichloroacetimidate (for benzylation of dimethyl malic ester under similar conditions, see: Keck et al. 1991; Christoffers and Rössler 2000; Bertus et al. 2003; Brimble et al. 2011) in the presence of triflic acid afforded the corresponding benzyl ether **8** in 98 % yield (Scheme 1).

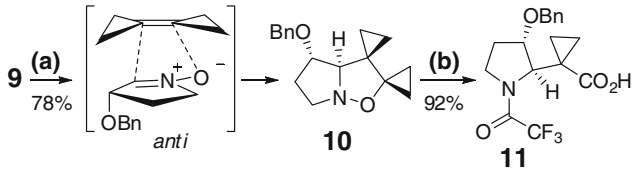
The 1,3-DC of nitrone **9** with BCP afforded exclusively isoxazolidine **10** derived from the addition of the symmetric dipolarophile to the nitrone *Re* face (Scheme 2). The observed diastereoselectivity proves that the 4-OBn group hinders the *Si* face of the pyrroline *N*-oxide with the same efficiency of the bulkier 4-O*t*Bu group when BCP is used as dipolarophile (Zorn et al. 1999). The cycloaddition was carried out at 60 °C to avoid the alternative thermal rearrangement of 5-spirocyclopropaneisoxazolidines that takes place under neutral conditions, affording 4-tetrahydropyridones (Zorn et al. 1999; Brandi et al. 2003; Cordero et al. 2004b). The conversion of nitrone **9** was monitored by TLC and was complete after 2 days.

Isoxazolidine **10** smoothly underwent ATR in the presence of a slight excess (1.5 equiv) of TFA giving homoproline **11** in high yield. The use of the OBn instead of the O*t*Bu protection was found to be highly beneficial, because the yield of ATR increased from 73 to 92 % (Cordero et al. 2009). The cyclopropane ring spirofused at C-3′ is found intact on the C-2 carbon of **11** after the rearrangement. In fact, this method is a general access to 2-cyclopropyl-β^3-homoprolines, compounds not easily available by other synthetic approaches but particularly interesting because of the well-known key role played by the cyclopropyl ring on reactivity, conformational freedom, and biological activity of various compounds including amino acids (Gnad and Reiser 2003; Brackmann and de Meijere 2007a, b). Finally, as a result of the *anti* TS in the cycloaddition step, 4-hydroxyl group on the pyrrolidine ring of **11** is *trans* oriented with respect to the substituent on C-2 analogously to HYP (Persikov et al. 2000; Berisio et al. 2002; Schumacher et al. 2006; Krane 2008; Gorres and Raines 2010).

Summing up (3*R*, 4*S*)-4-hydroxy-2-cyclopropyl-β^3-homoproline **11** was obtained through the two-step



Scheme 1 Synthesis of *O*-benzyl nitrone **9**



Scheme 2 Synthesis of β-homoproline **11** by 1,3-DC/ATR sequence. Reaction conditions: (a) BCP, toluene, 60 °C, 2 days; (b) TFA (1.5 equiv), CH_3CN, 70 °C (MW), 15 min

sequence 1,3-DC/ATR in 72 % overall yield and with total stereoselectivity.

In principle, the amino acid **11** could be directly used in peptidomimetic synthesis having a free carboxylic group and the nitrogen atom and the 4-OH function orthogonally protected. Actually, it is known that some synthetic amino acids react poorly or do not react at all with natural amino acids under standard reaction conditions. In this regard, a more substituted analog of **11** such as the 4,5-bis(benzyloxy)-6-(benzyloxymethy)-2-cyclopropyl-β^3 homoproline does not undergo intermolecular coupling at the pyrrolidine nitrogen atom. In that case, the lack of reactivity was overcome by reversing the common order of coupling in the synthesis of a mixed $\alpha/\beta/\alpha$ tripeptide and by performing the N-acylation intramolecularly (Cordero et al. 2009). Fortunately, the less substituted 4-benzyloxy-2-cyclopropyl-β^3-homoproline showed a regular reactivity of the nitrogen atom as proved by the synthesis of the α/β dipeptide **14** (Scheme 3). In particular, acid **11** was esterified with a bulky alcohol such as *tert*-butanol, and after N-deprotection was coupled with N-Fmoc valine under standard conditions to give **14** in 66 % yield.

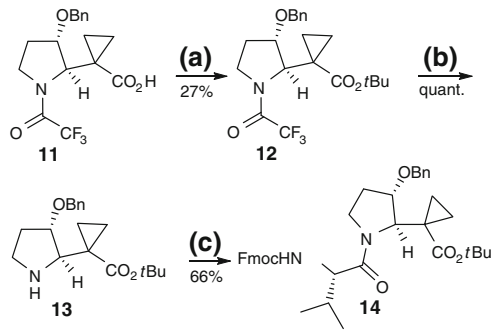
Accordingly, the synthesis of an $\alpha/\beta/\alpha$ tripeptide was studied following a standard approach (Scheme 4). Acid **11** smoothly reacted with Val-OMe to give dipeptide **15** in 83 % yield. Reductive removal of the trifluoroacetyl group afforded **16** that was coupled with Boc-Phe to get tripeptide **17** in 31 % yield. The reactivity of dipeptide **16** was poorer compared to ester **13**, likely due to the hindrance of the reactive site caused by the valine residue. This result suggests a reduced flexibility of **16** that could adopt a U-shaped conformation induced by the presence of the cyclopropyl group.

Having established that 2-cyclopropyl-β^3-homoproline **2** (R = Bn, R^1–R^2 = CH_2CH_2, Fig. 1) is a suitable building block for peptidomimetic synthesis, we sought to test the versatility of the 1,3-DC/ATR approach to 4-hydroxy-β^3-homoprolines by synthesizing a 2-mono-substituted derivative. The introduction of a 2-hydroxyethyl chain, that is, the lateral chain of Ser, appeared particularly interesting as the amino acid **2** (R^1 = H, R^2 = CH_2-CH_2OH, Fig. 1) can be considered as a mimetic of the dipeptide Pro-Ser deprived of the amide moiety and, moreover, the primary hydroxyl group could be used to introduce different substituents on C-2.

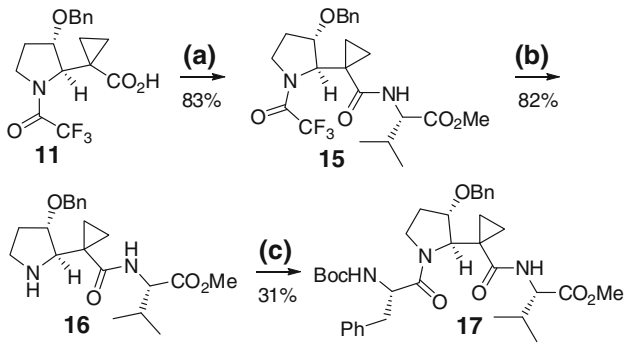
Alkoxycarbonyl-methylenecyclopropanes such as **19** are highly regioselective dipolarophiles in nitrone 1,3-DC reactions affording the required 4-alkoxycarbonyl-5-spirocyclopropanoisoxazolidines (Brandi et al. 1988, 1992; Cordero et al. 1993; Mauduit et al. 1998). A mixture of nitrone **18** and **19** gave the diastereomeric adducts **20a** and **20b** in 6:1 ratio and 81 % overall yield by heating at 30 °C overnight (Scheme 5) (see also Pisaneschi et al. 2006a).

By heating in the presence of TFA, the main adduct **20a** was converted into the malic acid derivative **21** that spontaneously undergoes decarboxylation under the reaction conditions affording the 2-unsubstituted β^3-homoproline **22** in low yield (Scheme 6).

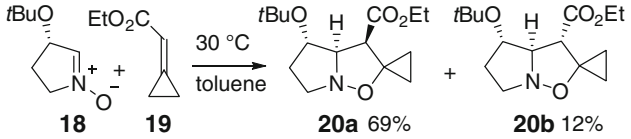
To avoid decarboxylation, the ester group in **20a** was selectively reduced with DIBAL (Scheme 7), and the 4-hydroxymethyl-isoxazolidine **23** and the corresponding acetate **24** were subjected to the ATR process. By heating in the presence of TFA, isoxazolidine **23** gave the expected homoproline **25** along with the N-deprotected amino acid **26** (Scheme 7). ^{1}H NMR analysis of the crude mixtures obtained under similar reaction conditions (70 °C, 5 min, CH_3CN) except for the amount of TFA showed that the



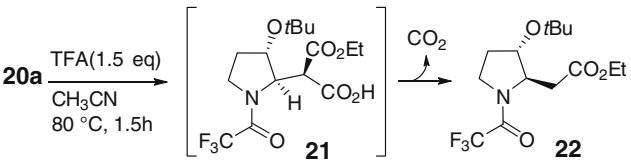
Scheme 3 Synthesis of the dipeptide **14**. Reaction conditions: (a) AcO*t*Bu, $HClO_4$; (b) $NaBH_4$, MeOH, rt; (c) Fmoc-Val, DIPEA, PyBrop, DMAP, CH_3CN



Scheme 4 Synthesis of the $\alpha/\beta/\gamma$ tripeptide **17**. Reaction conditions: (a) Val-OMe, EDCI, HOBt, CH_2Cl_2; (b) $NaBH_4$, MeOH, rt, 1.5 h; (c) Boc-Phe, DIPEA, PyBrop, DMAP, CH_3CN



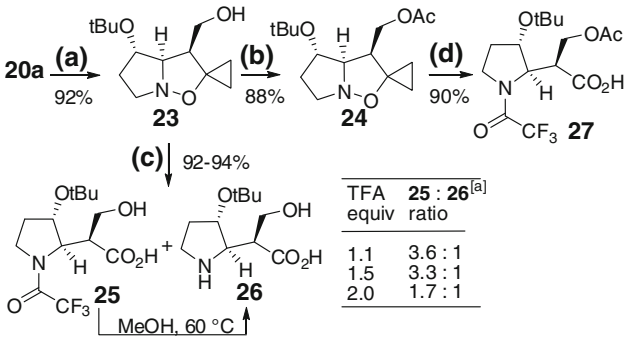
Scheme 5 1,3-DC of nitrone **18** with dipolarophile **19**



Scheme 6 ATR of isoxazolidine **20a**

25/26 ratio decreases by increasing TFA. The overall yield of **25** and **26** after chromatography was good (92–94 %) and did not change with the quantity of the acid used suggesting that a partial hydrolysis of **25** occurs under the ATR reaction conditions. The greater instability of the trifluoroacetamide group in **25** compared with other analog *N*-trifluoroacetyl-homoprolines can be rationalized considering an anchimeric assistance of the primary hydroxyl group. At the temperature necessary to induce the ATR process, **25** can undergo an intramolecular *6-exo-trig* trans-acylation with the formation of an easily hydrolysable trifluoroacetyl ester. The complete transformation of **25** into **26** by simple heating at 60 °C in MeOH confirmed this hypothesis (Scheme 7).

ATR of isoxazolidine **24**, having the acetylated hydroxymethyl group, occurred smoothly and with no surprises under standard conditions. Protected β^3-homoproline **27** was obtained in 90 % yield by heating a solution of protonated **24** at 70 °C for 2 min in a microwave oven (Scheme 7). The two-step 1,3-DC/ATR sequence allowed to obtain **27** in 62 % overall yield with control of the absolute configuration of the two new stereocenters C-2 and C-3.



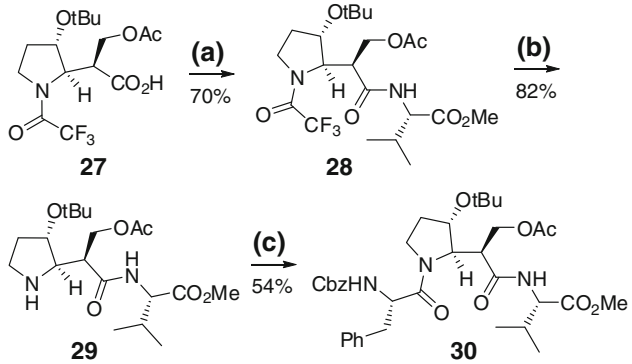
Scheme 7 Synthesis and ATR of isoxazolidines **23** and **24**. [a] Determined by ^{1}H NMR analysis of the crude mixture. Reaction conditions: (a) DIBAL; (b) Ac_2O, DMAP (cat); (c) TFA (1.1, 1.5 or 2 equiv), CH_3CN, 70 °C (MW), 5 min; (d) TFA (1.5 equiv), CH_3CN, 70 °C (MW), 2 min

It is worth to be noted that the cycloaddition of pyrroline *N*-oxides with 2,3-unsubstituted acrylic acid derivatives affords cycloadducts with the opposite regiochemistry, compared to **20**, leading to 2-hydroxy-3-(pyrrolidin-2-yl)propanoic acid derivatives after reduction of the N–O bond (Argyropoulos et al. 2007; Pisaneschi et al. 2006b; Salvati et al. 2005; Cordero et al. 2005; Sár et al. 2005, 2003). Only in one case, the formation of a little amount of a 2-(2-hydroxyethyl)-β^3-homoproline was reported (Mao et al. 2010).

The new homoproline **27** could be coupled at both the N- and C-terminus with α-amino acids without problems as showed in Scheme 8. Interestingly, N-acylation of dipeptide **29** occurred with a higher yield compared to the analog reaction on **16** (Schemes 4, 8), validating the constraint effect on the dipeptide conformation exerted by the cyclopropyl ring on C-2 of the β^3-homoproline.

Conclusions

The two-step sequence 1,3-DC/ATR applied to enantiopure pyrroline *N*-oxides easily derived from malic acid was proved to be a reliable and versatile approach to the interesting class of C-2-substituted 4-hydroxy-β^3-homoproline. The two synthesized homoprolines **11** and **27** could be directly inserted in mixed α/β/α tripeptides showing an acceptable reactivity at both the N- and C-terminus. The pyrrolidine nitrogen atom turned out to be particularly sensible to steric hindrance exerted by vicinal groups especially in the case of 2-cyclopropyl derivatives. These nitrogen reactivity properties indirectly suggest a good propensity of 2-cyclopropyl-homoprolines to induce reverse turns when inserted in peptides, whereas the 2-hydroxymethyl-homoproline can be regarded as a new non-hydrolysable Pro-Ser mimetic.



Scheme 8 Synthesis of the α/β/α tripeptide **30**. Reaction conditions: (a) Val-OMe, EDCI, HOBt, CH_2Cl_2; (b) $NaBH_4$, MeOH, rt, 1 h; (d) Cbz-Phe, DIPEA, PyBrop, DMAP, CH_3CN

The possibility of getting these β-amino acids through the process described above constitutes an important first step toward their potential applications in the peptidomimetic field and the study of the secondary structure of amino acid sequences containing them. Studies for the evaluation of biological and organocatalytic activity of the synthesized 4-hydroxy-β^3-homoprolines and peptides are in progress.

Experimental

General

Chemicals were purchased from Sigma-Aldrich and Alfa Aesar. BCP was synthesized as previously reported (de Meijere et al. 2002). Reactions anhydrous conditions were carried out under an atmosphere of nitrogen and the solvents were appropriately dried before use. Chromatographic purifications were performed on silica gel 60 (0.040–0.063 mm, 230–400 mesh ASTM, Merk) using flash-column technique; Rf values refer to TLC carried out on 0.25-mm silica gel plates with the same eluant indicated for column chromatography unless otherwise stated. All evaporations were carried out at reduced pressure. NMR spectra were recorded on Varian GEMINI 200, GEMINI 300, MERCURY 400, and INOVA 400 spectrometers using $CDCl_3$ solutions, unless otherwise stated, and were referenced internally to solvent reference frequencies. Assignments were made on the basis of ^{1}H–^{1}H COSY, HMQC, HSQC, and HMBC experiments. Mass spectra: MS (EI) were recorded on a QP5050 Shimadzu spectrometer with a GC (70-eV ionizing voltage); MS (ESI) were recorded on a LCQ Fleet Ion Trap Mass Spectrometer with Surveyor Plus LC System (Thermo Scientific) operating in positive ($^+$ESI) and negative ($^-$ESI) ion mode by direct infusion of a methanolic solution of the sample. Melting points (mp) were determined on an electrothermal apparatus and are not corrected. Polarimetric measurements were taken on a JASCO DIP-370. IR spectra were recorded with a PerkinElmer Spectrum BX FT-IR System spectrophotometer. Elemental analyses were performed with a PerkinElmer 2400 analyzer. Microwave-assisted reactions were carried out in a CEM Discover^{TM} single-mode microwave reactor with IR temperature sensor using an irradiation power of 150 W with simultaneous cooling.

Diethyl (2*S*)-2-(*benzyloxy*)*succinate* (**8**) Triflic acid (0.415 mL, 4.75 mmol) was added to a mixture of diethyl malate (753 mg, 3.96 mmol), benzyl trichloroacetimidate (2.0 g, 7.92 mmol), and 3 Å molecular sieves in anhydrous Et_2O (33 mL) under nitrogen atmosphere. The mixture was stirred for 15 h at rt, filtered, and washed with a saturated aq. Na_2CO_3 solution. The organic solution was dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by chromatography (petroleum ether/AcOEt = 10/1) afforded **8** (1.088 g, 98 %) as a colorless oil. **8**: $R_f = 0.31$ (petroleum ether/AcOEt = 10/1). $[\alpha]_D^{23} = -59.9$ ($c = 6.8$, $CHCl_3$). ^{1}H-NMR (400 MHz): $\delta = 7.38$–7.27 (m, 5H, Ar–*H*), 4.77 (d, $J = 11.4$ Hz, 1H, CH_2Ph), 4.55 (d, $J = 11.4$ Hz, 1H, CH_2Ph), 4.39 (dd, $J = 7.7$, 5.2 Hz, 1H, C*H*OBn), 4.27–4.10 (m, 4H, CH_3CH_2O), 2.82 (A part of an ABX system, $J = 16.0$, 5.2 Hz, 1H, OCHC*H*H), 2.76 (B part of an ABX system, $J = 16.0$, 7.7 Hz, 1H, OCHC*H*H), 1.30 (t, $J = 7.1$ Hz, 3H, CH_3) 1.24 (t, $J = 7.1$ Hz, 3H, CH_3). ^{13}C-NMR (50 MHz): $\delta = 171.3$ (s, *C*O), 169.9.0 (s, *C*O), 137.2 (s, Ar), 128.3 (d, 2C, Ar), 128.0 (d, 2C, Ar), 127.8 (d, Ar), 74.6 (d, CO*C*H), 73.0 (t, *C*H_2Ph), 61.2 (t, *C*H_2CH$_3$), 60.9 (t, *C*H_2CH$_3$), 38.1 (t, CO*C*H_2CH), 14.21 (q, *C*H_3), 14.16 (q, *C*H_3). IR ($CDCl_3$): $\nu = 3{,}031$, 2,984, 1,733, 1,376, 1,275, 1,179, 1,114, 1,028 cm^{-1}. $C_{15}H_{20}O_5$ (280.32): calcd. C 64.27, H 7.19; found C 64.04, H 7.25.

(3a′*R*,4′*S*)-4′-(*Benzyloxy*)*tetrahydrodispiro*[*cyclopropane*-1,2′-*pyrrolo*[1,2-b]*isoxazole*-3′,1″-*cyclopropane*] (**10**) A mixture of nitrone **9** (152 mg, 0.795 mmol) and BCP (140 mg, 1.75 mmol) in toluene (0.8 mL) was heated at 60 °C in a Sovirel tube for 2 days. The solvent was evaporated and the crude product was purified by chromatography (petroleum ether/AcOEt = 3/1) to give **10** (168 mg, 78 %) as a pale yellow oil. **10**: $R_f = 0.30$ (petroleum ether/AcOEt = 3/1). $[\alpha]_D^{23} = +26.7$ ($c = 0.8$, $CHCl_3$). ^{1}H-NMR (400 MHz): $\delta = 7.37$–7.27 (m, 5H, Ar–*H*), 4.51 (A part of an AB system, $J = 11.8$ Hz, 1H, C*H*HPh), 4.42 (B part of an AB system, $J = 11.8$ Hz, 1H, CH*H*Ph), 4.04 (pseudo dt, $J = 5.9$, 3.0 Hz, 1H, 4′-H), 3.56 (d, $J = 2.8$ Hz, 1H, 3a′-H), 3.46–3.40 (m, 2H, 6′-H), 2.25 (dddd, $J = 13.3$, 8.9, 7.7, 5.9 Hz, 1H, 5′-H$_a$), 1.91 (dddd, $J = 13.3$, 5.9, 4.9, 3.2 Hz, 1H, 5′-H$_b$), 0.86–0.68 (m, 4H, *c*-Pr), 0.66–0.60 (m, 1H, *c*-Pr), 0.48–0.37 (m, 1H, *c*-Pr), 0.25–0.13 (m, 2H, *c*-Pr) ppm. ^{13}C-NMR (100 MHz): $\delta = 138.0$ (s, Ar), 128.4 (d, 2C, Ar), 127.7 (d, Ar), 127.6 (d, 2C, Ar), 83.8 (d, C-4′), 78.4 (d, C-3a′), 71.1 (t, *C*H_2Ph), 66.3 (s, C-2′), 56.3 (t, C-6′), 30.9 (s, C-3′), 30.9 (t; C-5′), 11.4 (t, *c*-Pr), 10.1 (t, *c*-Pr), 4.63 (t, *c*-Pr), 4.59 (t, *c*-Pr) ppm. IR ($CDCl_3$): $\nu = 3{,}080$, 3,032, 3,002, 2,946, 1,454, 1,357, 1,179, 1,071, 1,027 cm^{-1}. MS (EI): *m*/*z* (%) = 271 (1) [M$^+$], 256 (1), 242 (1), 180 (15), 166 (2), 152 (13), 108 (6), 91 (100), 69 (14), 41 (25). $C_{17}H_{21}NO_2$ (271.35): calcd. C 75.25, H 7.80, N 5.16; found C 75.37, H 8.15, N 4.89.

1-[(2*R*,3*S*)-3-(*Benzyloxy*)-1-(*trifluoroacetyl*)*pyrrolidin*-2-*yl*] *cyclopropanecarboxylic acid* (**11**) A mixture of **10** (126 mg, 0.464 mmol) and TFA (55 L, 0.7 mmol) in CH_3CN (11.8 mL) was heated in the microwave reactor at 70 °C for 15 min. The reaction mixture was concentrated

and purified by chromatography (hexane/Et_2O = 1/1) to give **11** (153 mg, 92 %) as a pale yellow oil. **11**: $R_f = 0.32$ (hexane/Et_2O = 1/1). $[\alpha]_D^{23} = +28.2$ ($c = 0.8$, $CHCl_3$). ^{1}H-NMR (400 MHz): δ = 7.38–7.27 (m, 5H, Ar–*H*), 4.65 (A part of an AB system, $J = 12.0$ Hz, 1H, C*H*HPh), 4.59 (B part of an AB system, $J = 12.0$ Hz, 1H, CH*H*Ph), 4.35–4.32 (m, 1H, 2-H), 4.29–4.25 (m, 1H, 3-H), 3.96–3.86 (m, 1H, 5-H_a), 3.81–3.73 (m, 1H; 5-H_b), 2.28 (pseudo ddt, $J = 13.3$, 5.4, 8.2 Hz, 1H, 4-H_a), 2.10–2.00 (m, 1H, 4-H_b), 1.48 (ddd, $J = 9.8$; 7.4; 4.5 Hz, 1H, *c*-Pr), 1.31 (ddd, $J = 9.7$; 7.4; 4.5 Hz, 1H, *c*-Pr), 1.14 (ddd, $J = 9.8$; 7.4; 4.5 Hz, 1H, *c*-Pr), 0.96 (ddd, $J = 9.7$; 7.4; 4.5 Hz, 1H, *c*-Pr) ppm. ^{13}C-NMR (100 MHz): δ = 179.5 (s, *C*O_2H), 156.8 (q, $J_{CF} = 36.7$ Hz, *C*OCF_3), 137.8 (s, Ar), 128.5 (d, 2C, Ar), 127.8 (d, Ar), 127.6 (d, 2C, Ar), 116.3 (q, $J_{CF} = 288.0$ Hz, *C*F_3), 81.0 (d, C-3), 71.0 (t, *C*H_2Ph), 65.7 (d, C-2), 46.3 (tq, $J_{CF} = 3.8$ Hz, C-5), 31.0 (t, C-4), 23.9 (s, *c*-Pr), 15.9 (t, *c*-Pr), 14.7 (t, *c*-Pr) ppm. ^{19}F-NMR (188 MHz): $\delta = -77.2$ (s, 3F, C*F*$_3$) ppm. IR ($CDCl_3$): ν = 3,067, 2,912, 1,693, 1,454, 1,431, 1,205, 1,152 cm^{-1}. MS ($^+$ESI) *m/z* = 380.2 $[M + Na]^+$. MS ($^-$ESI) *m/z* = 356.3 $[M - H]^-$. $C_{17}H_8F_3NO_4$ (357.32): calcd. C 57.14, H 5.08, N 3.92; found C 57.41; H 5.17; N 4.23.

tert-Butyl 1-((2*R*,3*S*)-3-(*benzyloxy*)-1-{*N*-[(9*H-fluoren*-9-*ylmethoxy*)*carbonyl*]-L-*valyl*}*pyrrolidin*-2-*yl*)*cyclopropanecarboxylate* (**14**) A mixture of *β*-homoproline **11** (100 mg, 0.28 mmol) and $HClO_4$ (60 %, 11 μL, 0.1 mmol) in AcO*t*Bu (0.56 mL) was stirred at rt for 20 h, cooled at 0 °C, and treated dropwise with a saturated aq. $NaHCO_3$ solution (2.5 mL). After 10 min, the mixture was extracted with CH_2Cl_2 (4 × 3 mL). The combined organic phases were washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated. Filtration through silica gel (hexane/Et_2O = 15/1) gave *tert*-butyl ester **12** (31 mg, 27 %) as a yellow oil. {$R_f = 0.34$ (*n*-hexane/Et_2O = 15/1). ^{1}H-NMR (200 MHz): δ = 7.39–7.28 (m, 5H, Ar–*H*), 4.67 (A part of an AB system, $J = 11.8$ Hz, 1H, OC*H*HPh), 4.59 (B part of an AB system, $J = 11.8$ Hz, 1H, OCH*H*Ph), 4.41 (br s, 1H, 2-H), 4.29–4.22 (m, 1H, 3-H), 4.01–3.68 (m, 2H, 5-H), 2.42–2.20 (m, 1H, 4-H_a), 2.16–1.95 (m, 1H, 4-H_b), 1.41 [s, 9H, C(C*H*$_3$)$_3$], 1.38–1.23 (m, 1H, *c*-Pr), 1.13–1.00 (m, 1H, *c*-Pr), 0.99–0.84 (m, 1H, *c*-Pr), 0.84–0.70 (m, 1H, *c*-Pr) ppm. MS ($^+$ESI) *m/z* = 436.16 $[M + Na]^+$}. $NaBH_4$ (5.7 mg, 0.15 mmol) was added to a solution of **12** (31 mg, 0.075 mmol) in MeOH (1.5 mL) at 0 °C. The reaction mixture was stirred at rt for 6 h, treated with wet Na_2SO_4, stirred for further 20 min, and then filtered on Celite®. The solution was dried over Na_2SO_4, filtered, and concentrated to give pyrrolidine **13** (25 mg) as a yellow oil which was used without further purification. {$R_f = 0.12$ (hexane/Et_2O = 1/1). ^{1}H-NMR (200 MHz): δ = 7.40–7.22 (m, 5H, Ar–*H*), 4.59 (A part of an AB system, $J = 11.8$ Hz, 1H, OC*H*HPh), 4.49 (B part of an AB system, $J = 11.8$ Hz, 1H, OC*H*HPh), 3.92 (pseudo dt, $J = 4.9$, 4.3 Hz, 1H, 3-H), 3.12–2.88 (m, 3H, 2-H, 5-H_a, 5-H_b), 2.34 (br s, NH), 1.96–1.82 (m, 2H, 4-H), 1.40 [s, 9H, C(*C*H$_3$)$_3$], 1.20–1.00 (m, 2H, *c*-Pr), 0.99–0.76 (m, 2H, *c*-Pr) ppm. MS ($^+$ESI) *m/z* = 318.04 $[M + H]^+$, 340.12 $[M + Na]^+$}. 0PyBroP (70 mg, 0.150 mmol), DIPEA (26 L, 0.150 mmoli) and DMAP (4.6 mg, 0.038 mmol) were added to a mixture of **13** (25 mg, 0.075 mmol) and Fmoc-Val (51 mg, 0.150 mmol) in CH_3CN (0.4 mL) cooled at 0 °C. The reaction mixture was stirred at rt for 4 days and then concentrated. Purification by chromatography (hexane/AcOEt = 7/3) gave **14** (31.5 mg, 66 %) as a white waxy solid. **14**: $R_f = 0.2$ (hexane/AcOEt = 4/1). $[\alpha]_D^{23} = -6.5$ ($c = 0.5$, $CHCl_3$). Mixture of conformers [A major, B minor (detectable signals)]: ^{1}H-NMR (400 MHz): δ = 7.80–7.71 (m, 2H, Ar–*H*), 7.64–7.57 (m, 2H, Ar–*H*), 7.43–7.35 (m, 2H, Ar–*H*), 7.35–7.21 (m, 7H, Ar–*H*), 5.61 (br d, $J = 9.1$ Hz, NH, A), 4.87 (s, 1H, 2-H, B), 4.73 (A part of an AB system, $J = 12.0$ Hz, 2H, OC*H*HPh, B), 4.65 (B part of an AB system, $J = 12.0$ Hz, 2H, OCH*H*Ph, B), 4.62 (A part of an AB system, $J = 11.8$ Hz, 1H, OC*H*HPh, A), 4.58 (B part of an AB system, $J = 11.8$ Hz, 1H, OCH*H*Ph, A), 4.47–4.11 (m, 5H, 3-H, C*H*-*i*Pr, OC*H*$_2$Fmoc, C*H*Fmoc), 4.33 (br s, 1H, 2-H, A) 3.94–3.83 (m, 1H, 5-H_a, A), 3.77–3.60 (m, 1H, 5-H_b, A and 5-H_a, B), 3.45–3.36 (m, 1H, 5-H_b, B), 2.35–2.22 (m, 1H, 4-H_a), 2.10–1.93 (m, 2H, C*H*Me$_2$, 4-H_b), 1.46 [s, 9H, C(C*H*$_3$)$_3$, B], 1.40 [s, 9H, C(C*H*$_3$)$_3$, A], 1.34–1.19 (m, 2H, *c*-Pr), 0.99 (d, $J = 6.7$ Hz, 3H, C*H*$_3$), 0.90 (d, $J = 6.7$ Hz, 3H, C*H*$_3$), 0.95–0.79 (m, 2H, *c*-Pr, A), 0.77–0.66 (m, 1H, *c*-Pr, B), 0.46–0.37 (m, 1H, *c*-Pr, B) ppm. ^{13}C-NMR (50 MHz): δ = 172.3 (s, *C*O, A), 172.0 (s, *C*O, B), 171.9 (s, *C*O, B), 171.8 (s, *C*O, A), 156.3 (s, O*C*ONH, A), 155.8 (s, O*C*ONH, B), 143.9 (s, Ar), 143.8 (s, Ar), 141.2 (s, 2C, Ar), 138.1 (s, Ar), 128.3 (d, 2C, Ar), 127.5 (d, 5C, Ar), 127.0 (d, 2C, Ar),125.1 (d, 2C, Ar), 119.8 (d, 2C, Ar), 83.0 (d, C-3, B), 81.7 (d, C-3, A), 81.4 (s, *C*Me$_3$, B), 80.7 (s, *C*Me$_3$, A), 70.8 (t, O*C*H$_2$Ph, A), 70.5 (t, O*C*H$_2$Ph, B), 67.0 (t, O*C*H$_2$Fmoc, A), 66.8 (t, O*C*H$_2$Fmoc, B), 64.5 (d, C-2, A), 61.1 (d, C-2, B), 57.5 (d, *C*H-*i*Pr, B), 57.2 (d, *C*H-*i*Pr, A), 47.2 (t, C-5, A), 47.0 (d, *C*HFmoc), 46.0 (t, C-5, B), 32.2 (d, *C*HMe$_2$, B), 31.6 (d, *C*HMe$_2$, A), 30.8 (t, C-4), 28.1 [q, 3C, C(*C*H$_3$)$_3$], 25.7 (s, *c*-Pr, B), 25.2 (s, *c*-Pr, A), 19.8 (q, CH*C*H$_3$), 17.1 (q, CH*C*H$_3$) 13.8 (t, *c*-Pr, A), 13.2 (t, *c*-Pr, A), 12.2 (t, *c*-Pr, B), 09.2 (t, *c*-Pr, B) ppm. IR ($CDCl_3$): ν = 3427, 3068, 2970, 1715, 1643, 1507, 1143 cm^{-1}. MS ($^+$ESI) *m/z* = 661.39 $[M + Na]^+$. $C_{39}H_{46}N_2O_6$ (638.79): calcd. C, 73.33; H, 7.26; N, 4.39; O, 15.03; found C, 72.99; H, 7.30; N, 4.08; O, 15.63.

Methyl *N*-({1-[(2*R*,3*S*)-3-(*benzyloxy*)-1-(*trifluoroacetyl*)*pyrrolidin*-2-*yl*]*cyclopropyl*}*carbonyl*)-L-*valinate* (**15**) A mixture of *β*-homoproline **11** (65 mg, 0.182 mmol), *N*-(3-

dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDCI, 70 mg, 0.364 mmol), and 1-hydroxybenzotriazole (HOBt, 49 mg, 0.364 mmol) in dry CH_2Cl_2 (0.750 mL) was stirred at 0 °C for 20 min. In a separate flask, a mixture of Val-OMe HCl (55 mg, 0.328 mmol) and Et_3N (0.037 mL, 0.364 mmol) in CH_2Cl_2 (0.650 mL) was stirred for 15 min and then added to the activated β-homoproline. The reaction mixture was stirred at rt for 23 h and then filtered through a short pad of silica gel (CH_2Cl_2/MeOH = 60/1) to give **15** (71 mg, 83 %) as a yellow oil. **15**: $R_f = 0.33$ (CH_2Cl_2/MeOH = 60/1). ^{1}H-NMR (400 MHz): $\delta = 7.37–7.25$ (m, 5H, Ar–*H*), 6.43 (br d, $J = 8.4$ Hz, NH), 4.60 (A part of an AB system, $J = 11.7$ Hz, 1H, OC*H*HPh), 4.52 (B part of an AB system, $J = 11.7$ Hz, 1H, OCH*H*Ph), 4.45–4.40 (m, 1H, 3-H), 4.44 (dd, $J = 8.4$, 4.9 Hz, 1H, C*H*-*i*Pr), 4.11 (br s, 1H, 2-H), 3.91–3.82 (m, 1H, 5-H_a), 3.72 (s, 3H, OCH_3), 3.79–3.68 (m, 1H, 5-H_b), 2.27 (pseudo ddt, $J = 13.7$, 5.2, 8.5 Hz, 1H, 4-H_a), 2.13 (d septet, $J = 4.9$, 6.9 Hz, 1H, C*H*Me$_2$), 2.10–1.99 (m, 1H, 4-H_b), 1.29–1.20 (m, 1H, *c*-Pr), 1.10–0.99 (m, 1H, *c*-Pr), 0.77 (m, 1H, *c*-Pr), 0.91 (d, $J = 6.9$ Hz, 3H, CH_3), 0.88 (d, $J = 6.9$ Hz, 3H, CH_3), 0.77 (ddd, $J = 9.7$; 6.8; 5.3 Hz, 1H, *c*-Pr) ppm. ^{13}C-NMR (50 MHz): $\delta = 172.2$ (s, *C*O), 172.0 (s, *C*O), 156.8 (q, $J_{CF} = 36.8$ Hz, *C*OCF$_3$), 137.7 (s, Ar), 128.4 (d, 2C, Ar), 127.8 (d, Ar), 127.7 (d, 2C, Ar), 116.2 (q, $J_{CF} = 287.7$ Hz, *C*F$_3$), 81.6 (d, *C*H-*i*Pr), 71.2 (t, O*C*H$_2$Ph), 68.7 (d, C-2), 57.3 (d, C-3), 52.1 (q, O*C*H$_3$), 46.3 (dt, $J_{CF} = 3.6$ Hz, C-5), 30.9 (d, *C*HMe$_2$), 30.7 (t, C-4), 27.4 (s, *c*-Pr), 18.8 (q, CH*C*H$_3$), 17.7 (q, CH*C*H$_3$) 13.0 (t, *c*-Pr), 11.1 (t, *c*-Pr) ppm. ^{19}F-NMR (188 MHz): $\delta = -72.3$ (s, 3F, C*F*$_3$) ppm. IR ($CDCl_3$): $\nu = 3438$, 3032 2968, 1738, 1690, 1511, 1438, 1207, 1153 cm^{-1}. MS ($^+$ESI) *m/z* = 493.3 [M + Na]$^+$. MS ($^-$ESI) *m/z* = 469.5 [M − H]$^-$.

Methyl N-({1-[(2*R*,3*S*)-3-(*benzyloxy*)*pyrrolidin*-2-*yl*]*cyclopropyl*}*carbonyl*)-L-*valinate* (**16**) $NaBH_4$ (10.5 mg, 0.276 mmol) was added at 0 °C to a solution of dipeptide **15** (65 mg, 0.138 mmol) in MeOH (2.8 mL). The reaction mixture was stirred at rt for 1.5 h, treated with wet Na_2SO_4, stirred for further 20 min, and then filtered on Celite®. The solution was dried over Na_2SO_4, filtered, and concentrated to give **16** (47 mg, 82 %) as a yellow oil which was used in the next step without further purification. **16**: $R_f = 0.47$ (CH_2Cl_2/MeOH = 25/1). ^{1}H-NMR (400 MHz): $\delta = 9.77$ (br d, $J = 8.2$ Hz, N*H*CO), 7.37–7.23 (m, 5H, Ar–*H*), 4.54 (A part of an AB system, $J = 11.6$ Hz, 1H, OC*H*HPh), 4.47 (dd, $J = 8.2$, 4.6 Hz, 1H, C*H*-*i*Pr), 4.46 (B part of an AB system, $J = 11.6$ Hz, 1H, OCH*H*Ph), 4.06 (ddd, $J = 7.8$, 5.7, 3.0 Hz, 1H, 3-H), 3.69 (s, 3H, CH_3O), 3.15 (pseudo dt, $J = 2.3$, 9.5 Hz, 1H, 5-H_a), 3.01 (pseudo dt, $J = 7.6$, 9.5 Hz, 1H, 5-H_b), 2.57 (d, $J = 5.7$ Hz, 1H, 2-H), 2.12 (dqq, $J = 4.6$, 7.4, 7.2 Hz, 1H, C*H*Me$_2$), 2.08–1.96 (m, 1H, 4-H_a), 1.94–1.81 (m, 1H, 4-H_b), 1.47 (ddd, $J = 9.5$, 6.6, 3.9 Hz, 1H, *c*-Pr), 0.96 (ddd, $J = 9.5$, 6.6, 3.7 Hz, 1H, *c*-Pr), 0.89 (d, $J = 7.2$ Hz, 3H, CHCH_3), 0.87 (d, $J = 7.4$ Hz, 3H, CHCH_3), 0.80 (ddd, $J = 9.3$, 6.6, 3.9 Hz, 1H, *c*-Pr), 0.60 (ddd, $J = 9.3$, 6.6, 3.7 Hz, 1H, *c*-Pr), ppm. ^{13}C-NMR (100 MHz): $\delta = 173.6$ (s, *C*O), 172.8 (s, *C*O), 138.1 (s, Ar), 128.4 (d, 2C, Ar), 127.7 (d, Ar), 127.6 (d, 2C, Ar), 81.7 (d, C-3), 72.0 (t, O*C*H$_2$Ph), 70.4 (d, C-2), 57.4 (d, *C*H-*i*Pr), 51.8 (q, O*C*H$_3$), 44.4 (t, C-5), 31.3 (t, C-4), 30.8 (d, *C*HMe$_2$), 23.7 (s, *c*-Pr), 19.4 (q, CH*C*H$_3$), 18.0 (q, CH*C*H$_3$), 15.0 (t, *c*-Pr), 09.9 (t, *c*-Pr) ppm. IR ($CDCl_3$): $\nu = 3{,}348$, 3,174, 3,031, 2,967, 1,738, 1,653, 1,541, 1,437, 1,259, 1,211, 1,095 cm^{-1}. MS ($^+$ESI) *m/z* = 375.22 [M + H]$^+$, 397.28 [M + Na]$^+$. MS ($^-$ESI) *m/z* = 373.61 [M − H]$^-$.

Methyl N-[(1-{(2*R*,3*S*)-3-(*benzyloxy*)-1-[*N*-(*tert-butoxycarbonyl*)-L-*phenylalanyl*]*pyrrolidin*-2-*yl*}*cyclopropyl*)*carbonyl*]-L-*valinate* (**17**) Following the same procedure as for **14**, tripeptide **17** (23 mg, 31 %) was obtained as a white waxy solid starting from **16** (46 mg, 0.122 mmol) and Boc-Phe (49 mg, 0.183 mmol) (reaction time, 5 days). **17**: $R_f = 0.44$ (CH_2Cl_2/CH_3CN = 15/1). Mixture of conformers [A major, B minor (detectable signals)]: ^{1}H-NMR (400 MHz): $\delta = 7.37–7.01$ (m, 10H, Ar–*H*), 7.15 (br d, $J = 7.6$ Hz, Val-*N*HCO, A), 7.09 (br d, $J = 7.3$ Hz, Val-*N*HCO, B), 5.31 (br d, $J = 9.5$ Hz, Phe-*N*HCO, B), 5.26 (br d, $J = 8.8$ Hz, Phe-*N*HCO, A), 4.91–4.81 (m, 1H, C*H*CH$_2$Ph, B), 4.80–4.70 (m, 1H, C*H*CH$_2$Ph, A), 4.67 (br s, 1H, 2-H, A), 4.59 (d, $J = 11.7$ Hz, 1H, OCH*H*Ph), 4.53–4.32 (m, $2H_A + 3H_B$, OCH*H*Ph, *C*H-*i*Pr, A + B and 3-H, B), 4.22 (br s, 1H, 2-H, B), 4.15–4.08 (m, 1H, 3-H, A), 3.86–3.76 (m, 1H, 5-H_a, A), 3.73 (s, 3H, OCH_3, B), 3.69 (s, 3H, OCH_3, A), 3.69–3.59 (m, 1H, 5-H_a, B), 3.38–3.27 (m, 1H, 5-H_b, B), 3.24–3.13 (m, 1H, 5-H_b, A), 3.05–2.80 (m, 2H, CHCH_2Ph), 2.19–1.83 (m, 3H, C*H*Me$_2$, 4-H), 1.38 [s, 9H, C(*C*H$_3$)$_3$, A], 1.35 [s, 9H, C(*C*H$_3$)$_3$, B], 1.19–1.08 (m, 1H, *c*-Pr, A), 0.92 (d, $J = 6.8$ Hz, 3H, CH_3), 0.91 (d, $J = 6.8$ Hz, 3H, CH_3), 0.80–0.73 (m, 1H, *c*-Pr, A), 0.58–0.46 (m, 1H, *c*-Pr, B), 0.46–0.28 (m, 2H, *c*-Pr, A) ppm. ^{13}C-NMR (100 MHz): $\delta = 172.9$ (s, *C* = O), 172.5 (s, *C* = O), 172.2 (s, *C* = O), 154.9 (s, O*C*ONH), 138.0 (s, Ar), 136.4 (s, Ar), 129.4 (d, 2C, Ar), 128.5 (d, 2C, Ar), 128.3 (d, 2C, Ar), 127.7 (d, Ar), 127.6 (d, 2C, Ar), 126.9 (d, 1C, Ar), 83.5 (d, C-3, B), 81.9 (d, C-3, A), 79.7 (s, *C*Me$_3$), 70.7 (t, O*C*H$_2$Ph), 60.0 (d, C-2), 57.6 (d, *C*H-*i*Pr), 53.1 (d, *C*HCH$_2$Ph), 52.0 (q, O*C*H$_3$), 46.4 (t, C-5, A), 45.6 (t, C-5, B), 39.9 (t, O*C*H$_2$Ph), 30.9 (d, *C*HMe$_2$), 30.5 (t, C-4), 28.3 [q, 3C, C(*C*H$_3$)$_3$], 27.3 (s, *c*-Pr), 19.0 (q, CH*C*H$_3$), 18.0 (q, CH*C*H$_3$), 12.5 (t, *c*-Pr, A), 10.1 (t, *c*-Pr, A), 09.8 (t, *c*-Pr, B), 08.7 (t, *c*-Pr, B) ppm. IR ($CDCl_3$): $\nu = 3{,}435$, 3,318, 3,031, 2,970, 1,739, 1,703, 1,647, 1,498, 1,437, 1,368, 1,166 cm^{-1}. MS ($^+$ESI) *m/z* = 644.32 [M + Na]$^+$. MS ($^-$ESI) *m/z* = 620.55 [M − H]$^-$.

Ethyl [(2*R*,3*S*)-3-*tert-butoxy*-1-(*trifluoroacetyl*)*pyrrolidin*-2-*yl*]*acetate* (**22**) A mixture of **20a** (50.4 mg, 0.178 mmol) and TFA (21 μL, 0.27 mmol) in CH_3CN (5.9 mL) was heated at 80 °C for 1.5 h. The reaction mixture was concentrated and purified by chromatography (CH_2Cl_2/MeOH = 20/1) to give **22** (15 mg, 26 %). **22**: $R_f = 0.22$ (AcOEt). ^{1}H-NMR (400 MHz): $\delta = 4.15$ (q, $J = 7.1$ Hz, 2H, CH_2Me), 3.88 (pseudo q, $J = 6.4$ Hz, 1H, 3-H), 3.39 (ddd, $J = 8.7$, 6.4, 4.5 Hz, 1H, 2-H), 3.33–3.18 (m, 2H, 5-H), 2.74 (A part of an ABX system, $J = 16.7$, 4.5 Hz, 1H, 6-H_a), 2.67 (B part of an ABX system, $J = 16.7$, 8.7 Hz, 1H, 6-H_b), 2.19–2.10 (m, 1H, 4-H_a), 1.82–1.73 (m, 1H, 4-H_b), 1.26 (t, $J = 7.1$ Hz, 3H, CH_2CH_3), 1.18 [s, 9H, C(CH_3)$_3$] ppm. IR ($CDCl_3$): ν = 2,978, 2,934, 1,728, 1,681, 1,392, 1,367, 1,192, 1,145 cm^{-1}.

[(3′*S*,3a′*R*,4′*S*)-4′-*tert-Butoxytetrahydro*-3′*H*-*spiro*[*cyclopropane*-1,2′-*pyrrolo*[1,2-*b*]*isoxazol*]-3′-*yl*]*methanol* (**23**) A 1 M solution of DIBAL-H in hexane (3.2 mL, 3.2 mmol) was added dropwise to a solution of the adduct **20a** (261 mg, 0.92 mmol) in CH_2Cl_2 (3.1 mL) under nitrogen atmosphere at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then treated in sequence with MeOH and a saturated aq. sodium and potassium tartrate solution. The aqueous phase was extracted with CH_2Cl_2 and the organic extracts were dried over Na_2SO_4. Evaporation of the solvent and purification by chromatography gave crude **23** (222 mg) which was used in the next step without further purification. Purification of a small amount of the crude compound (50 mg) by chromatography (Et_2O/petroleum ether = 10/1) afforded analytically pure **23** (46 mg, 92 %) as a white solid. **23**: $R_f = 0.30$ (Et_2O/petroleum ether = 10/1). $[\alpha]_D^{24} = -47.3$ ($c = 0.6$, $CHCl_3$). mp 80–81 °C. ^{1}H-NMR (400 MHz): $\delta = 4.52$ (q, $J = 7.2$ Hz, 1H, 4′-H), 3.82 (pseudo dt, $J = 2.0$, 10.6 Hz, 1H, C*H*H-OH), 3.72 (t, $J = 7.4$ Hz, 1H, 3a′-H), 3.49 (ddd, $J = 13.7$, 8.9, 4.9 Hz, 1H, 6′-H_a), 3.46 (pseudo dt, $J = 5.5$, 10.4 Hz, 1H, CH*H*-OH), 3.24 (dt, $J = 13.7$, 7.6 Hz, 1H, 6′-H_b), 3.19 (ddd, $J = 10.4$, 7.4, 5.5 Hz, 1H, 3′-H), 2.86 (dd, $J = 10.4$, 2.4 Hz, 1H, OH), 2.32 (dddd, $J = 12.5$, 7.6, 7.2, 4.9, 1H, 5′-H_a), 1.78 (ddt, $J = 12.5$, 8.9, 7.6 Hz, 1H, 5′-H_b), 1.27 [s, 9H, C(CH_3)$_3$], 0.92 (ddd, $J = 11.4$, 6.7, 5.5 Hz, 1 H, *c*-Pr), 0.77 (ddd, $J = 11.4$, 7.2, 6.1 Hz, 1H, *c*-Pr), 0.70–0.64 (m, 1 H; *c*-Pr), 0.48 (ddd, $J = 10.5$, 7.2, 5.5 Hz, 1H, *c*-Pr) ppm. ^{13}C-NMR (50 MHz): $\delta = 75.2$ (d, C-3a′), 75.0 (s, *C*Me$_3$), 72.6 (d, C-4′), 62.7 (s, C-2′), 60.8 (t, *C*H$_2$OH), 54.7 (t, C-6′), 48.9 (d, C-3′), 34.0 (t, C-5′), 28.7 [q, 3C, C(*C*H$_3$)$_3$], 9.2 (t, *c*-Pr), 6.9 (t, *c*-Pr) ppm. IR (KBr): ν = 3,158, 2,968, 2,930, 1,367, 1,358, 1,196, 1,172, 1,062, 1,035, 1,021, 805 cm^{-1}. MS (EI): *m/z* (%) = 241 (2.4) [M$^+$], 184 (4), 154 (9), 126 (11), 112 (17), 98 (9), 82 (12), 68 (23), 57 (100). $C_{13}H_{23}NO_3$ (241.33): calcd. C 64.70, H 9.61, N 5.80; found C 64.98, H 9.66, N 5.68.

[(3′*S*,3a′*R*,4′*S*)-4′-*tert-Butoxytetrahydro*-3′*H*-*spiro*[*cyclopropane*-1,2′-*pyrrolo*[1,2-*b*]*isoxazol*]-3′-yl]*methyl acetate* (**24**) Acetic anhydride (3.4 mL, 38.5 mmol) was added to a solution of crude isoxazolidine **23** (470 mg) and a catalytic amount of DMAP in pyridine (9.5 mL) under nitrogen atmosphere at 0 °C. The reaction mixture was stirred at rt overnight, treated with MeOH (5 mL) at 0 °C for 30 min, and then concentrated. The crude product was dissolved in CH_2Cl_2 (10 mL) and washed with 5 % aq. $NaHCO_3$ solution (10 mL). The aqueous solution was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated. Purification by chromatography (Et_2O/hexane = 4/1) gave **24** (486 mg, 88 %) as colorless oil. **24**: $R_f = 0.30$ (Et_2O/*n*-hexane = 4/1). $[\alpha]_D^{23} = -20.5$ ($c = 0.8$, $CHCl_3$). ^{1}H-NMR (400 MHz): $\delta = 4.26$–4.21 (m, 1H, 4′-H), 4.23 (dd, $J = 11.3$, 6.7 Hz, 1H, C*H*H-OAc), 4.06 (dd, $J = 11.3$, 7.6 Hz, 1H, CH*H*-OAc), 3.77 (dd, $J = 8.0$, 4.2 Hz, 1H, 3a′-H), 3.38–3.23 (m, 2H, 6′-H), 3.10 (pseudo q, $J = 7.5$ Hz, 1H, 3′-H), 2.18 (dddd, $J = 12.8$, 9.0, 7.4, 6.4 Hz, 1H, 5′-H_a), 2.05 (s, 3H, CH_3C = O), 1.73 (dddd, $J = 12.8$, 6.9, 4.5, 3.8 Hz, 1H, 5′-H_b), 1.20 [s, 9H, C(CH_3)$_3$], 0.97–0.91 (m, 1H, *c*-Pr), 0.82–0.77 (m, 2H, *c*-Pr), 0.59–0.53 (m, 1H, *c*-Pr) ppm. ^{13}C-NMR (50 MHz): $\delta = 170.5$ (s, *C*OMe), 76.2 (d, C-3a′), 73.9 (s, *C*Me$_3$), 72.2 (d, C-4′), 64.0 (s, C-2′), 62.7 (t, *C*H$_2$-OAc), 55.2 (t, C-6′), 45.7 (d, C-3′), 34.6 (t, C-5′), 28.6 [q, 3C, C(*C*H$_3$)$_3$], 20.8 (q, CO*C*H$_3$), 9.3 (t, *c*-Pr), 6.8 (t, *c*-Pr) ppm. IR ($CDCl_3$): ν = 2,979, 1,738, 1,366, 1,243, 1,235, 1,217, 1,214, 1,210, 1,036 cm^{-1}. MS (EI): *m/z* (%) = 283 (0.8) [M$^+$], 226 (1), 210 (0.3), 198 (0.3), 166 (18), 156 (7), 112 (16), 110 (10), 82 (10), 68 (20), 57 (100). $C_{15}H_{25}NO_4$ (283.36): calcd. C 63.58, H 8.89, N 4.94; found C 63.21, H 8.82, N 4.62.

(2*S*)-2-[(2*R*,3*S*)-3-*tert-Butoxy*-1-(*trifluoroacetyl*)*pyrrolidin*-2-*yl*]-3-*hydroxypropanoic acid* (25) *and* (2*S*)-2-[(2*R*,3*S*)-3-*tert-butoxypyrrolidin*-2-*yl*]-3-*hydroxypropanoic acid* (**26**) A mixture of **23** (31 mg, 0.128 mmol) and TFA (15 μL, 0.26 mmol) in CH_3CN (4.3 mL) was heated in the microwave reactor at 70 °C for 5 min. The reaction mixture was concentrated and purified by chromatography (AcOEt/MeOH from 10/1 to 5/1) to give **25** (23.3 mg, 56 %) and **26** (11.4 mg, 38 %). **25**: $R_f = 0.30$ (AcOEt/MeOH = 10/1). ^{1}H-NMR (400 MHz, CD_3OD): $\delta = 4.33$–4.29 (m, 2H, 2-H, 3-H), 3.87–3.70 (m, 3H, 7-H_a, 5-H), 3.65 (dd, $J = 11.0$, 4.7 Hz, 1H, 7-H_b), 2.78–2.73 (m, 1H, 6-H), 2.30 (ddt, $J = 13.6$, 4.5, 9.5 Hz, 1H, 4-H_a), 1.98–1.90 (m, 1H, 4-H_b), 1.21 [s, 9H, C(CH_3)$_3$] ppm. ^{13}C-NMR (50 MHz, CD_3OD): $\delta = 176.1$ (s, *C*O_2H), 158.3 (q, $J_{CF} = 36.4$ Hz, *C*OCF$_3$), 117.7 (q, $J_{CF} = 285.0$ Hz, *C*F$_3$), 76.0 (s, *C*Me$_3$),

73.1 (d, C-3), 67.5 (d, C-2), 62.2 (t, C-7), 49.0 (d, C-6), 46.2 (q, $J_{CF} = 4.6$ Hz, C-5), 33.4 (t, C-4), 28.7 [q, 3C, C(CH_3)$_3$] ppm. ^{19}F-NMR (188 MHz, CD_3OD): $\delta = -76.9$ ppm. MS (EI): *m/z* (%) = 327 (0.2) [M^+], 271 (4), 253 (10), 236 (11), 218 (5), 202 (3), 182 (11), 178 (7), 166 (10), 140 (5), 126 (5), 96 (6), 69 (21), 57 (100). **26**: $R_f = 0.19$ (AcOEt/MeOH = 10/1). ^{1}H-NMR (400 MHz, CD_3OD): $\delta = 4.34$ (pseudo dt, $J = 5.6$, 3.6 Hz, 1H, 3-H), 4.00 (A part of an ABX system, $J = 11.0$, 4.7 Hz, 1H, 7-H_a), 3.91 (B part of an ABX system, $J = 11.0$, 6.9 Hz, 1H, 7-H_b), 3.72 (dd, $J = 5.6$, 4.1 1H, 2-H), 3.42–3.29 (m, 2H, 5-H), 2.63–2.55 (m, 1H; 6-H), 2.20 (pseudo ddt, $J = 13.7$, 5.6, 8.3 Hz, 1H, 4-H_a), 1.96–1.83 (m, 1H, 4-H_b), 1.22 [s, 9H, C(CH_3)$_3$] ppm. ^{13}C-NMR (200 MHz, CD_3OD): $\delta = 177.6$ (s, CO_2H), 76.2 (s, *C*Me$_3$), 73.4 (d, C-3), 68.2 (d, C-2), 62.8 (t, C-7), 49.0 (d, C-6), 44.7 (t, C-5), 34.3 (t, C-4), 28.9 [s, 3C, C(*C*H$_3$)$_3$] ppm. MS ($^+$ESI) *m/z* = 254.12 [M + Na]$^+$. MS ($^-$ESI) *m/z* = 230.27 [M − H]$^-$.

(2*S*)-3-(*Acetyloxy*)-2-[(2*R*,3*S*)-3-*tert-butoxy*-1-(*trifluoroacetyl*)*pyrrolidin*-2-yl]*propanoic acid* (**27**) A mixture of **24** (79 mg, 0.279 mmol) and TFA (32 μL, 0.42 mmol) in CH_3CN (9.2 mL) was heated in the microwave reactor at 70 °C for 2 min. The reaction mixture was concentrated and purified by chromatography (CH_2Cl_2/MeOH = 20/1) to give **27** (92.2 mg, 90 %). **27**: $R_f = 0.29$ (CH_2Cl_2/MeOH = 20/1). $[\alpha]_D^{23} = -10.6$ ($c = 0.8$, $CHCl_3$). ^{1}H-NMR (400 MHz, CD_3OD): $\delta = 4.36$–4.31 (m, 2H, 2-H, 3-H), 4.35 (dd, $J = 11.2$, 8.0 Hz, 1H, 7-H_a), 4.15 (dd, $J = 11.2$, 5.9 Hz, 1H, 7-H_b), 3.89–3.81 (m, 1H, 5-H_a), 3.78–3.69 (m, 1H, 5-H_b), 3.03 (pseudo dt, $J = 5.9$, 8.0 Hz, 1H, 6-H), 2.29 (pseudo ddt, $J = 13.6$, 4.7, 9.2 Hz, 1H, 4-H_a), 2.01 (s, 3H, COCH_3), 1.99–1.92 (m, 1H, 4-H_b), 1.21 [s, 9H, C(CH_3)$_3$] ppm. ^{1}H-NMR (400 MHz): $\delta = 4.42$ (dd, $J = 11.3$, 7.9 Hz, 1H, 7-H_a), 4.37–4.32 (m, 1H, 2-H), 4.24–4.21 (m, 1H, 3-H), 4.19 (dd, $J = 11.3$, 6.2 Hz, 1H, 7-H_b), 3.91–3.82 (m, 1H; 5-H_a), 3.67 (ddd, $J = 10.5$, 8.8, 4.6 Hz, 1H, 5-H_b), 3.24–3.19 (m, 1H, 6-H), 2.23–2.14 (m, 1H, 4-H_a), 2.05 (s, 3H, COCH_3), 1.96–1.87 (m, 1H, 4-H_b), 1.19 [s, 9H, C(CH_3)$_3$] ppm. ^{13}C-NMR (50 MHz): $\delta = 175.0$ (s, CO_2H), 170.6 (s, *C*OCH$_3$), 156.4 (q, $J_{CF} = 37.0$ Hz, *C*OCF$_3$), 116.1 (q, $J_{CF} = 287.5$ Hz, *C*F$_3$), 74.9 (s, *C*Me$_3$), 71.3 (d, C-3), 65.6 (d, C-2), 62.0 (t, C-7), 45.5 (q, $J_{CF} = 3.7$ Hz, C-5), 45.4 (t, C-6), 33.0 (t, C-4), 28.3 [q, 3C, C(CH_3)$_3$], 20.7(q, COCH_3) ppm. ^{19}F-NMR (188 MHz, CD_3OD): $\delta = -73.7$ ppm. IR ($CDCl_3$): ν = 3,492, 2,977, 2,935, 1,741, 1,714, 1,689, 1,449, 1,392, 1,366, 1,243, 1,154 cm^{-1}. MS (EI): *m/z* (%) = 314 (0.9), 295 (1), 254 (10), 235 (21), 218 (15), 203 (11), 184 (7), 175 (7), 161 (15), 57 (100). MS ($^+$ESI) *m/z* = 392.25 [M + Na]$^+$. MS ($^-$ESI) *m/z* = 368.21 [M − H]$^-$. $C_{15}H_{22}F_3NO_6$ (369.33): calcd. C 48.78, H 6.00, N 3.79; found C 49.12, H 6.33, N 3.73.

Methyl N-{(2*S*)-3-(*acetyloxy*)-2-[(2*R*,3*S*)-3-*tert-butoxy*-1-(*trifluoroacetyl*)*pyrrolidin*-2-*yl*]*propanoyl*}-L-*valinate* (**28**) Following the same procedure as for **15**, dipeptide **28** (60 mg, 70 %) was obtained as a white waxy solid starting from β-homoproline **27** (60 mg, 0.162 mmol). **28**: $R_f = 0.48$ (CH_2Cl_2/MeOH = 5/1). ^{1}H-NMR (400 MHz): $\delta = 6.30$ (br d, J = 8,6 Hz, NH), 4.62–4.57 (m, 1H, 3-H), 4.46 (dd, $J = 8.6$, 4.9 Hz, 1H, C*H*-*i*Pr), 4.36 (dd, $J = 11.1$, 9.0 Hz, 1H 7-H_a), 4.24 (dd, $J = 11.1$, 5.6 Hz, 1H, 7-H_b), 4.17 (dd, $J = 5.6$, 2.6 Hz, 1H, 2-H), 3.87–3.78 (m, 1H, 5-H_a), 3.72 (s, 3H, OCH_3), 3.59 (ddd, $J = 10.6$, 7.9, 5.6 Hz, 1H, 5-H_b), 3.38 (pseudo dt, $J = 9.0$, 5.6 Hz, 1H, 6-H), 2.04 (s, 3H, CH_3C = O) 2.19 (pseudo ddt, $J = 13.0$, 5.1, 7.9 Hz, 1H, 4-H_a), 2.11 (dseptet, $J = 5.0$, 6.9 Hz, 1H, C*H*Me$_2$), 1.87–1.77 (m, 1H, 4-H_b), 1.19 [s, 9H, C(CH_3)$_3$], 0.90 (d, $J = 6.9$ Hz, 3H, CH_3), 0.87 (d, $J = 6.9$ Hz, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz): $\delta = 171.7$ (s, *C*O$_2$Me), 170.7 (s, *C*ONH), 170.4 (s, CH$_3$*C*O), 156.3 (q, $J_{CF} = 36.8$ Hz, *C*OCF$_3$), 116.1 (q, $J_{CF} = 287.4$ Hz, *C*F$_3$), 74.8 (s, *C*Me$_3$), 70.8 (d, C-3), 66.2 (d, C-2), 63.0 (t, C-7), 57.4 (d, *C*H-*i*Pr), 52.2 (q, O*C*H$_3$), 46.4 (d, C-6), 46.0 (dt, $J_{CF} = 3.4$ Hz, C-5), 33.5 (t, C-4), 30.9 (d, *C*HMe$_2$), 28.5 [q, 3C, C(*C*H$_3$)$_3$], 20.7 (q, *C*H$_3$CO), 18.8 (q, CH*C*H$_3$), 17.7 (q, CH*C*H$_3$) ppm. ^{19}F-NMR (188 MHz): $\delta = -72.1$ (s, 3F, C*F*$_3$) ppm. IR ($CDCl_3$): ν = 3,420, 2,973, 1,740, 1,687, 1,511, 1,438, 1,365, 1,245, 1,206, 1,152 cm^{-1}. MS (EI): *m/z* (%) = 483 (0.4) [M^+], 125 (11), 111 (19), 97 (33), 71 (50), 57 (100), 43 (95), 41 (46). MS ($^+$ESI) *m/z* = 483.1 [M + H]$^+$.

Methyl N-{(2*S*)-3-(*acetyloxy*)-2-[(2*R*,3*S*)-3-*tert-butoxypyrrolidin*-2-*yl*]*propanoyl*}-L-*valinate* (**29**) $NaBH_4$ (11.2 mg, 0.295 mmol) was added to a solution of **28** (71.2 mg, 0.147 mmol), in MeOH (2.9 mL) at 0 °C. The reaction mixture was stirred at rt for 1 h, concentrated, cooled at 0 °C, diluted with H_2O (5 mL), and extracted with AcOEt (4 × 5 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Filtration through a short pad of silica gel (AcOEt) afforded **29** (47 mg, 82 %) as a waxy solid. **29**: $R_f = 0.32$ (AcOEt). ^{1}H-NMR (400 MHz): $\delta = 8.34$ (br d, $J = 9.0$ Hz, N*H*CO), 5.85–5.74 (m, 1H, N*H*), 4.55 (dd, $J = 9.0$, 5.5 Hz, 1H, C*H*-*i*Pr), 4.41 (d, $J = 3.9$ Hz, 1H, 3-H), 4.20 (d, $J = 11.8$ Hz, 1H, 2-H), 3.78–3.61 (m, 2H, 7-H_a, 5-H_a), 3.68 (s, 3H, CH_3O), 3.55 (dm, $J = 12.7$ Hz, 1H, 7-H_b), 3.45 (pseudo t, $J = 9.6$ Hz, 1H, 5-H_b), 2.29–2.08 (m, 2H, 4-H_a, C*H*Me$_2$), 2.15 (s, 3H, CH_3C = O), 1.95–1.81 (m, 2H, 6-H, 4-H_b), 1.08 [s, 9H, C(CH_3)$_3$], 0.94 (d, $J = 7.0$ Hz, 3H, CHCH_3), 0.93 (d, $J = 7.09$ Hz, 3H, CHCH_3) ppm. ^{13}C-NMR (50 MHz): $\delta = 173.0$ (s, *C*OMe), 172.5 (s, *C*ONH), 171.6 (s, *C*O$_2$Me), 74.5 (s, *C*Me$_3$), 72.0 (d, C-3), 63.8 (d, C-2), 58.9 (t, C-7), 57.0 (d, *C*H-*i*Pr), 51.9 (q, O*C*H$_3$), 51.5 (d, C-6), 46.8 (t, C-5), 31.8

(t, C-4), 31.6 (d, *C*HMe$_2$), 28.1 [q, 3C, C(*C*H$_3$)$_3$], 22.5 (q, CO*C*H$_3$), 19.1 (q, CH*C*H$_3$), 17.8 (q, CH*C*H$_3$) ppm. IR (CDCl$_3$): ν = 3,309, 2,969, 2,891, 1,741, 1,659, 1,619, 1,534, 1,462, 1,437, 1,392, 1,366, 1,259, 1,205, 1,190, 1,096 cm^{-1}. MS ($^+$ESI) *m/z* = 387.21 [M + H]$^+$, 409.45 [M + Na]$^+$.

Methyl N-[(2*S*)-3-(*acetyloxy*)-2-((2*R*,3*S*)-1-{*N*-[(*benzyloxy*)*carbonyl*]*phenylalanyl*}-3-*tert-butoxypyrrolidin*-2-*yl*)*propanoyl*]-L-*valinate* (**30**) Following the same procedure as for **14**, tripeptide **30** (39 mg, 54 %) was obtained as a white waxy solid starting from **29** (42 mg, 0.109 mmol) and *N*-Cbz-Phe (49 mg, 0.163 mmol) (reaction time: overnight). **30**: R_f = 0.32 (CH$_2$Cl$_2$/CH$_3$CN = 2/1). $[\alpha]_D^{23} = -13.9$ (c = 0.74, CHCl$_3$). ^{1}H-NMR (400 MHz): δ = 7.37–7.18 (m, 10H, Ar–*H*), 7.13–7.07 (m, 2H, Ar–*H*), 6.82 (br d, J = 8.7 Hz, Val-*N*HCO), 5.32 (br d, J = 8.2 Hz, Phe-*N*HCO), 5.07 (A part of an AB system, J = 12.3 Hz, 1H, OC*H*HPh), 5.03 (B part of an AB system, J = 12.3 Hz, 1H, OCH*H*Ph), 4.68–4.59 (m, 1H, C*H*CH$_2$Ph), 4.45 (dd, J = 8.7, 5.3 Hz, 1H, *C*H-*i*Pr), 4.39 (dd, J = 10.7, 4.7 Hz, 1H, 7-H$_a$), 4.36–4.27 (m, 2H, 3-H, 7-H$_b$) 4.13 (d, J = 5.5 Hz, 1H 2-H), 3.65–3.51 (m, 1H, 5-H$_a$), 3.55 (s, 3H, C*H*$_3$O), 3.45–3.33 (m, 1H, 5-H$_b$), 3.24–3.15 (m, 1H, 6-H), 3.19 (X part of an AXY system, J = 13.8, 5.3 Hz, 1H, CHC*H*HPh), 3.00 (Y part of an AXY system, J = 13.8, 6.8 Hz, 1H, CHCH*H*Ph), 2.20–2.02 (m, 2H, 4-H$_a$, C*H*Me$_2$), 2.07 (s, 3H, C*H*$_3$C = O), 1.84–1.71 (m, 1H, 4-H$_b$), 1.73 [s, 9H, C(C*H*$_3$)$_3$], 0.93 (d, J = 6.8 Hz, 3H, CHC*H*$_3$), 0.93 (d, J = 6.8 Hz, 3H, CHC*H*$_3$) ppm. ^{13}C-NMR (100 MHz): δ = 172.1 (s, *C*O$_2$Me), 171.7 (s, Val-*C*ONH), 171.1 (s, Phe-*C*ONH), 170.9 (s, *C*OMe), 155.8 (s, O*C*ONH) 136.2 (s, Ar), 135.7 (s, Ar), 129.3 (d, 2C, Ar), 128.6 (d, 2C, Ar), 128.4 (d, 2C, Ar), 128.1 (d, 2C, Ar), 128.0 (d, 2C, Ar), 127.0 (d, 2C, Ar), 74.6 (s, *C*Me$_3$), 72.6 (d, C-3), 66.9 (t, CH*C*H$_2$Ph), 64.4 (d, C-2), 64.4 (t, C-7), 57.4 (d, *C*H-*i*Pr), 54.9 (d, *C*HCH$_2$Ph), 52.0 (q, O*C*H$_3$), 48.4 (d, C-6), 46.7 (t, C-5), 37.7 (t, O*C*H$_2$Ph), 32.8 (t, C-4), 30.5 (d, *C*HMe$_2$), 28.4 [q, 3C, C(*C*H$_3$)$_3$], 22.7 (q, CO*C*H$_3$), 19.1 (q, CH*C*H$_3$), 17.9 (q, CH*C*H$_3$) ppm. IR (CDCl$_3$): ν = 3,427, 3,065, 3,032, 2,969, 2,935, 1,738, 1,720, 1,674, 1,633, 1,509, 1,437, 1,417, 1,391, 1,347, 1,256, 1,193, 1,081, 1,057, cm^{-1}. MS ($^+$ESI) *m/z* = 690.46 [M + Na]$^+$. $C_{36}H_{49}N_3O_9$ (667.79): calcd. C, 64.75; H, 7.40; N, 6.29; O, 21.56; found C, 64.48; H, 7.03; N, 6.31; O, 22.63.

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