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Synthesis of Chiral Scaffolds Based on Polyfunctional Cyclobutane β-Amino Acids

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In Memory of Ferenc Fülöp.

Chiral scaffolds have been synthesized through selective transformations from conveniently protected cyclobutane β-amino acids. The obtained derivatives present additional functional groups, such as hydroxyl, carboxyl, or carbon-carbon triple bond, linked to the amino acid core through a flexible C_1 or C_2 alkyl fragment. The resultant molecules are highly versatile to be used as chiral precursors for the production of polyfunctional chemical platforms. These can be suitable for the synthesis of complex molecules, through condensation reactions, such as peptide coupling, dehydration between a carboxylic acid and an alcohol, or click chemistry. To illustrate some of these possibilities, two hybrid tripeptides have been prepared as examples of their synthetic potential.

Introduction

Amino acids, along with carbohydrates and terpenes, are important contributors to the "chiral pool".[1] Actually, natural and unnatural or modified amino acids can act as building blocks in the construction of many attractive molecules that include bioactive natural products, pharmaceuticals, and chirons for complex architectures.[1,2,3]

Cyclobutane amino acids (CBAAs) are an interesting class of molecules that include both naturally occurring[4] and synthetic products and, accordingly, many efforts have been devoted to the preparation and applications of cyclobutane α-,[5] β-,[6,7] and γ-amino acids.[8–11] In particular, the derivatives obtained from (*R,S*)- and (*S,S*)-2-aminocyclobutane-1-carboxylic acids ((*R,S*)- and (*S,S*)-β-CBAA, respectively)[6,7] (Figure 1) have been revealed as powerful synthetic precursors of manifold products. When incorporated in homo or hybrid peptides, β-CBAAs can be useful as chiral polyfunctional platforms to produce different products as well as soft materials with specific features. In addition, the rigid cyclobutane moiety promotes the restriction of the molecular conformational freedom, which is an interesting factor concerning the properties of the target compounds.[12] Some selected instances are illustrated as follows. (*R,S*)- and (*S,S*)-β-CBAA were combined with L-proline affording hybrid α,β-tripeptides, which have been used as organocatalysts for enantioselective aldol additions.[13] Moreover, they have served as precursors for the synthesis of ligands for metal catalysis as well.[14] In other cases, β-CBAAs were key structural units to build peptidic organogelators resulting from their combination with themselves[15] or with linear monomers.[16] They were also used as a self-assembly component in functional organic fibers.[17] Regarding biomedical applications, cell penetrating peptides with ability to translocate the HeLa cell membrane have been obtained through the coupling of (*S,S*)-β-CBAA with N^{α}-functionalized 4-amino-L-proline (Figure 1).[18] Otherwise, the inclusion of β-CBAAs in the neuropeptide Y (NPY) significantly improved its selectivity; NPY controls central and peripheral processes by activation of the G protein coupled receptors Y_XR.[19] Analogues of its C-terminal fragment containing β-CBAAs displayed exclusively binding to Y_4R while the parental peptide shows promiscuous binding among different receptors of this family.[20] Furthermore, some β-CBAA-based cationic surfactants have been revealed as DNA-condensing agents with enhanced properties and absence of cell toxicity, making them promising candidates to be used as vectors in gene therapy.[21]

Otherwise, hydroxy-modified (*S,S*)-β-CBAA has been incorporated in conformationally constrained pyrrolidinyl peptide nucleic acids (PNA)[22] that exhibited improved binding with respect to the parent PNA.[23] Indeed, further functionalization of β-CBAA provide polyfunctional small molecules, which are interesting scaffolds for the construction of complex chiral structures.[24]

Now, in this work, we present the synthesis of β-CBAAs containing an additional functional group (FG, Figure 1) linked to the amino acid through a flexible C_1 or C_2 spacer. As representative examples, a primary alcohol, a carboxylic acid, and a terminal alkyne have been chosen as targets because of their versatility to be transformed into different functions or for

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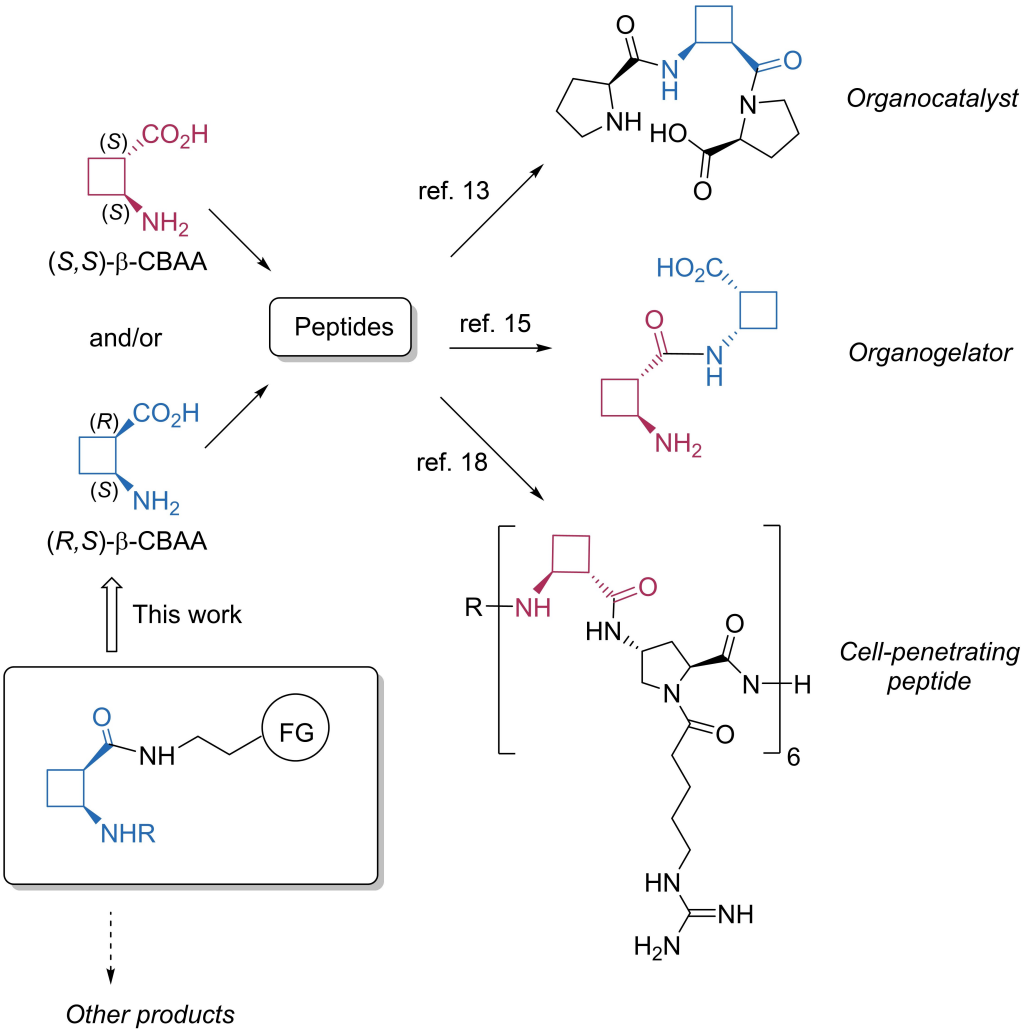

Figure 1. (*R,S*)- and (*S,S*)-β-CBAA as synthetic precursors of some peptide derivatives with defined properties, and general structure of the target molecules in this work.

the coupling with other structural units via condensation processes or, in the case of alkynes, to be used in click chemistry.[25] Moreover, the terminal alkyne group has been discovered in natural products made by plants, fungi and microorganisms and, recently, a pathway for terminal-alkyne amino acid biosynthesis has been reported.[26] Then, these amino acids have been utilized to prepare hybrid tripeptides providing polyfunctional chemical platforms suitable for building more elaborated compounds.

Results and Discussion

Scheme 1 shows the synthesis of the target molecules from precursor monoprotected amino acids **1** and **2**. They were coupled with glycine (Gly) that afforded the C_2 linker. Thus, reaction of **1**[7a] and **2**[7b] with MeO-Gly hydrochloride, in the presence of (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP), afforded fully protected compound **3** (83% yield), which was previously described,[27] and new product **4** (quantitative), respectively. Subsequently, separate reduction of the methyl ester with lithium borohydride ($LiBH_4$) in methanol at 0° C gave alcohols **5** and **6** in good yields. Unprotected amino alcohol **7** was then obtained in quantitative manner by hydrogenolysis of the benzyl carbamate (Cbz) in **5** in the presence of palladium hydroxide on charcoal. Alternatively, **7** was prepared by acidolysis of the *tert*-butyl carbamate (Boc) in **6** using trifluoroacetic acid (TFA). Otherwise, mild saponification of the methyl ester in **3** with 0.25 M sodium hydroxide provided quantitatively carboxylic acid **8**,[28] which was later used in peptide coupling reactions (see below).

In order to introduce the terminal triple bond, two strategies were assayed. The first one is based on the reaction of an aldehyde with a dimethyl diazophosphonate to create the triple bond affording the terminal carbon atom, also known as the Ohira-Bestmann modification of the Seyferth-Gilbert homologation.[29]

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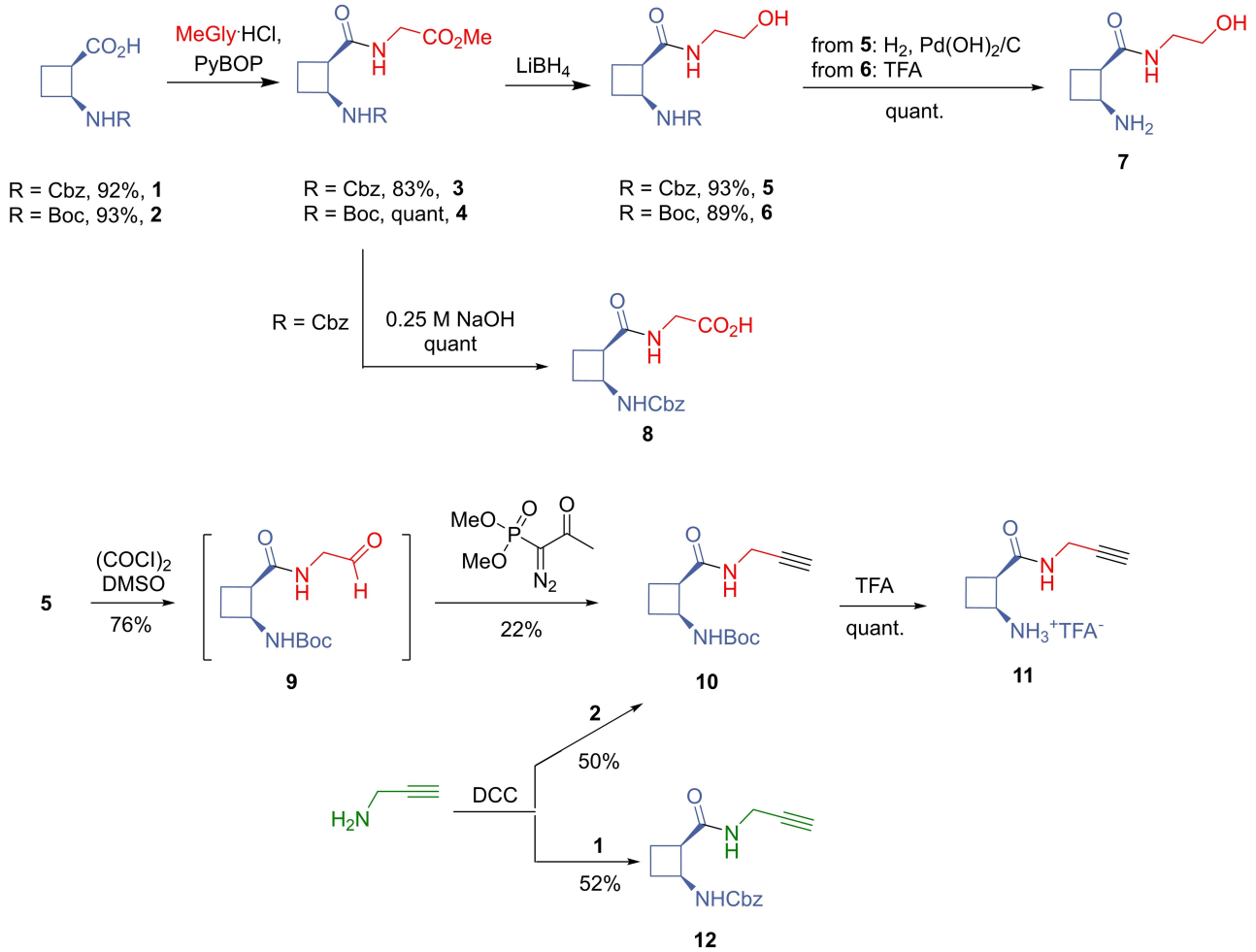
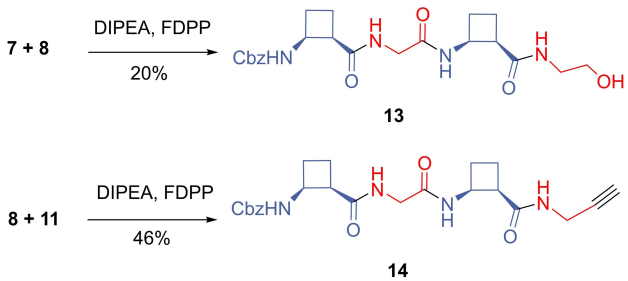


Scheme 1. Synthesis of the polyfunctional cyclobutane monomers.

Thus, alcohol **5** was oxidized with oxalyl chloride in the presence of dimethyl sulfoxide (DMSO) to afford aldehyde **9** in 76% yield, which was used in the next step without further purification. Subsequent reaction with dimethyl (1-diazo-2-oxopropyl)phosphonate (Bestmann-Ohira reagent)[30] provided alkyne **10** in 22% yield. Finally, quantitative acidolysis of Boc carbamate with TFA gave the ammonium salt **11**, in 17% overall yield from **5**, which was identified by its ^{1}H NMR spectroscopic data and used in subsequent reactions without purification. The yield was improved changing the synthetic strategy by coupling propargyl amine with carboxylic acids **1** and **2**, respectively, in the presence of *N,N'*-dicyclohexylcarbodiimide (DCC). In this way, compounds **11** and **12** were prepared in ca. 50% overall yield through a much shorter synthetic sequence.

To show the ability of these modified β-CBAA derivatives to produce peptide-based polyfunctional platforms, compounds **13** and **14** were synthesized (Scheme 2).

Thus, amine **7** was coupled with acid **8** using FDPP in the presence of Hünig base (diisopropylethylamine, DIPEA) to provide hydroxy peptide **13** as the only defined product, in 20% yield after careful purification (see the Experimental Section). The reaction was chemoselective and the compound



Scheme 2. Synthesis of the new peptide derivatives **13** and **14**.

resulting from the possible coupling of the acid with the primary alcohol was not detected. On the other hand, coupling of acid **8** with the free amine liberated in situ from ammonium salt **11**, afforded the peptide derivative **14** bearing a terminal triple bond, in 46% yield. Both compounds **13** and **14** have terminal functions, protected amine and alcohol or triple bond, allowing their inclusion into complex molecules via coupling reactions or, for instance, click chemistry.

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Conclusion

By means of selective transformations and starting from conveniently protected cyclobutane β-amino acids, the production of derivatives bearing a flexible fragment that contains additional functions, such as a primary alcohol, carboxylic acid, or terminal alkyne, has been achieved. The introduced functional groups confer these molecules with the possibility to be used as chiral scaffolds for the production of polyfunctional chemical platforms suitable for the synthesis of complex molecules, through condensation reactions or click chemistry. Two hybrid tripeptides have been prepared as some examples to illustrate the synthetic potential of these compounds.

Experimental Section

General Information: Starting amino acid **2**[7b] and dipeptide **3**[27] were prepared according to previously reported methods. Conventional chemicals were purchased from Sigma-Aldrich. Triethylamine (Et_3N) and *N*,*N*-Diisopropylethylamine (DIPEA) were distilled from a KOH solution before use. Solvents were used as received from the suppliers, unless otherwise stated. DCM and MeOH were dried prior to use by distillation under nitrogen from solutions with $CaCl_2$ and CaH_2, respectively. Dimethylformamide (DMF) was dried using 4 Å molecular sieves overnight and subsequent distillation under vacuum and low temperature. Melting points were determined with a Kofler apparatus. Optical rotations were measured using a JASCO-715 spectropolarimeter at 22 ± 2 °C. IR spectra of solids were recorded using a Sapphire-ATR Sensor 27 Bruker spectrophotometer. Silica gel 60 for flash chromatography (mean pore diameter: 60 Å; particle size: 0.04–0.06 mm, 230–400 mesh ASTM) was purchased from Scharlau. NMR spectra were acquired at 298 K on a AC250 Bruker spectrometer or a AVANCE360 Bruker spectrometer in $CDCl_3$ or CD_3OD solution. The ^1H and ^{13}C chemical shifts are given relative to TMS in ppm.

Methyl 2-((1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclobutanecarboxamido) acetate (4): A flask containing deprotected amino acid **2**[7b] (1.11 g, 5.16 mmol, 1.0 eq) and PyBOP (2.98 g, 5.72 mmol, 1.1 eq) was deoxygenated with N_2. 20 mL of DCM and DIPEA (3.67 mL, 21.08 mmol, 4.1 eq) were added and the mixture was stirred for 5 min. Glycine methyl ester hydrochloride (0.64 g, 5.72 mmol, 1.1 eq) was added and the resulting mixture was stirred at room temperature for 18 h. After, the solvent was removed, and the residue was purified by column chromatography from EtOAc (R_f = 0.48). Compound **4** was isolated as a white crystalline solid (1.47 g, 5.14 mmol, 99% yield). $[\alpha]_D$ −78.8 (c 1, MeOH). m.p. 103 °C (EtOAc). ^1H-NMR (360 MHz, $CDCl_3$) δ 1.40 (s, 9H), 1.84–1.99 (m, 1H), 1.99–2.14 (m, 1H), 2.15–2.38 (m, 2H), 3.29 (m, 1H), 3.75 (s, 3H), 3.96 (dd, $^2J_{H-H}$ = 18.3 Hz, $^3J_{H-H}$ = 5.0 Hz, 1H), 4.10 (dd, $^2J_{H-H}$ = 18.3 Hz, $^3J_{H-H}$ = 5.7 Hz, 1H), 4.35–4.48 (m, 1H), 5.47 (br.d, 1H), 6.17 (s, 1H). ^{13}C-NMR (90 MHz, $CDCl_3$) δ 18.1, 28.1, 29.3, 41.0, 45.9, 52.1, 79.1, 155.0, 170.1, 173.2. HRMS (ESI): $C_{13}H_{22}N_2NaO_5$ requires 309.1426, found $[M+Na]^+$309.1419. IR (ATR) 3336, 2955, 1770, 1683, 1650, 1520, 1513 cm^{-1}.

Benzyl (1*S*,2*R*)-2-(2-hydroxyethylcarbamoyl)cyclobutylcarbamate (5): A flask containing compound **3**[27] (0.1 g, 0.31 mmol, 1.0 eq) was deoxygenized with N_2. Et_2O (11 mL) was added, and the resulting solution was cooled down to 0 °C. 2 M $LiBH_4$ in THF (0.34 mL, 0.68 mmol, 2.2 eq) was added slowly to the mixture, causing the appearance of a white precipitate. The reaction mixture was stirred for 3 h at 0 °C until the entire reagent reacted (monitored by TLC). Subsequently, sat. $NH_4Cl_{(aq)}$ (15 mL) was slowly added and the mixture stirred for 15 min until gas development generally ceased. After, H_2O (15 mL) was added and the aqueous layer was extracted with EtOAc (4 × 15 mL). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated. Compound **5** was obtained in high purity as a white crystalline solid (85 mg, 0.29 mmol, 93% yield. R_f = 0.33, EtOAc:MeOH (20 : 1)). m.p. 77–78 °C (EtOAc). ^1H-NMR (400 MHz, $CDCl_3$) δ 1.84–2.04 (m, 1H), 2.09–2.20 (m, 1H), 2.21–2.45 (m, 2H), 2.66 (br.s, 1H), 3.15–3.34 (m, 2H), 3.35–3.48 (m, 1H), 3.54–3.68 (m, 2H), 4.39–4.57 (m, 1H), 5.04–5.13 (br. s, 2H), 5.75 (br. s, 1H), 6.11 (br. s, 1H), 7.30–7.46 (m, 5H).^{13}C-NMR (100 MHz, $CDCl_3$) δ 18.1, 28.6, 42.1, 46.1, 46.8, 61.9, 66.7 128.0, 128.1, 128.4, 136.3, 156.0, 173.6. HRMS (ESI): $C_{15}H_{20}N_2NaO_4$ requires 315.1320, found $[M+Na]^+$315.1316. IR (ATR) 3307, 3036, 2954, 2876, 1689, 1650, 1523 cm^{-1}.

***tert*-Butyl (1*S*,2*R*)-2-(2-hydroxyethylcarbamoyl)cyclobutylcarbamate (6)**: A flask containing compound **4** (0.60 g, 2.10 mmol, 1.0 eq) was deoxygenated with N_2. Et_2O (60 mL) was added and the flask cooled down to 0 °C. 2 M $LiBH_4$ in THF (2.5 mL, 5.03 mmol, 2.4 eq) was added slowly to the mixture, causing the appearance of a white precipitate. The reaction mixture was stirred for 3 h at 0 °C until the entire ester reacted (monitored by TLC). Subsequently, sat. $NH_4Cl_{(aq)}$ (40 mL) was slowly added and the mixture stirred for 15 min. After, H_2O (20 mL) was added and the aqueous layer was extracted with EtOAc (4 × 15 mL). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated. Compound **6** was obtained in high purity as a white crystalline solid (0.48 g, 1.86 mmol, 89% yield. R_f = 0.16, EtOAc). $[\alpha]_D$ −103.6 (c 1, MeOH). m.p. 142 °C (EtOAc). ^1H-NMR (360 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.86–2.00 (m, 1H), 1.85–2.71 (m, 4H), 3.21–3.29 (m, 1H), 3.39–3.48 (m, 2H),3.70–3.75 (m, 2H), 4.42 (ddd, $^3J_{H-H}$ = 8.4 Hz, 1H), 5.31 (br. s, 1H), 6.10 (br. s, 1H). ^{13}C-NMR (90 MHz, $CDCl_3$) δ 18.0, 28.3, 28.8, 42.2, 46.3, 62.0, 79.6, 155.6, 173.7. HRMS (ESI): $C_{12}H_{22}N_2NaO_4$ requires 281.1477, found $[M+Na]^+$281.1473. IR (ATR) 3363, 2946, 1675, 1630, 1545, 1509 cm^{-1}.

(1*R*,2*S*)-2-amino-*N*-(2-hydroxyethyl)cyclobutanecarboxamide (7): Compound **5** (0.12 g, 0.41 mmol) was dissolved in EtOAc (20 mL). $Pd(OH)_2$ on activated carbon (20 wt%, 0.02 g) was added and the mixture was stirred under a hydrogen atmosphere for 16 h (p = 6 bar). The reaction mixture was filtered through Celite®, washed with EtOAc and MeOH and dried. Compound **7** was obtained in quantitative yield in form of a white wax (0.06 g, 0.41 mmol). ^1H-NMR (250 MHz, $CDCl_3$) δ 1.81–2.45 (m, 4H), 3.04–3.82 (m, 6H), 6.86 (br. s, 1H). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ 18.4, 32.0, 42.7, 46.8, 49.4, 61.5, 174.5.

***tert*-Butyl (1*S*,2*R*)-2-(2-oxoethylcarbamoyl)cyclobutylcarbamate (9)**: Oxalyl chloride (0.43 mL, 0.85 mmol, 1.1 eq) was dissolved in anhydrous DCM and cooled down to −60 °C. DMSO (0.12 mL, 1.70 mmol, 2.2 eq) was added slowly to the oxalyl chloride mixture. The mixture was stirred for 2 min. Compound **5** (0.20 g, 0.77 mmol, 1.0 eq) was dissolved in a mixture of DMSO (0.2 mL) and DCM (1.7 mL) and subsequently added to the "activated" DMSO during 3 min. The white mixture was stirred for 15 min. After, Et_3N (0.54 g, 3.87 mmol, 5.0 eq) was slowly added and the resulting solution was stirred for 5 min. Then, the mixture was allowed to warm to room temperature (45 min) and a yellow, opaque liquid was obtained. Water (30 mL) was added and the mixture extracted with DCM (3 × 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and filtered. After the evaporation of the solvent, compound **9** was obtained as a yellowish solid (0.15 g, 0.59 mmol, 76% yield), which was used without further purification in the following step. ^1H-NMR (250 MHz, $CDCl_3$) δ 1.41 (s, 9H), 1.75–2.45 (m, 4H), 3.05–3.54 (m, 1H), 3.99–4.21 (m, 1H), 4.24–4.54 (m, 2H), 5.40 (br. d, $^3J_{H-H}$ = 7.8 Hz, 1H), 6.45 (br. s, 1H), 9.64 (s, 1H).

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***tert*-Butyl (1*S*,2*R*)-2-(prop-2-ynylcarbamoyl)cyclobutylcarbamate (10)**: Compound **9** (0.42 g, 1.64 mmol, 1.0 eq) was placed in a dry flask under a nitrogen atmosphere and dissolved in anhydrous MeOH (16 mL). K_2CO_3 (0.54 g, 3.93 mmol, 2.4 eq) and Bestmann-Ohira reagent (10 mol% in acetonitrile, 1.22 mL, 1.97 mmol, 1.2 eq) were added. The opaque mixture was stirred for 17.5 h at room temperature. After, the solvent was evaporated, the orange residue dissolved in Et_2O (12 mL) and washed with H_2O (100 mL) and sat. $NaHCO_{3(aq)}$ solution (50 mL). The aqueous layers were additionally extracted with Et_2O (2×20 mL) and DCM (2×20 mL). The organic layers were dried over $MgSO_4$ and the solvent was evaporated. The solid residue was purified by column chromatography from EtOAc: Hex (2:1) (R_f=0.46) yielding compound **10** in form of a white solid (0.09 g, 0.36 mmol, 22% yield). $[\alpha]_D$: −83.8 (c 0.4, DCM). m.p. 150–153 °C (EtOAc). ^{1}H-NMR (250 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.81–2.42 (m, 5H), 3.16–3.31 (m, 1H), 3.93–4.17 (m, 2H), 4.40 (m, 1H), 5.34 (br. d, $^3J_{H-H}$=8.1 Hz, 1H), 5.99 (br. s, 1H). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ 17.8, 28.1, 28.9, 29.4, 46.0, 46.1, 71.2, 77.0, 79.2, 155.1, 172.3. HRMS (ESI): $C_{13}H_{20}N_2NaO_3$ requires 275.1366, found $[M+Na]^+$275.1368. IR (ATR) 3354, 3325, 2994, 2971, 2919, 2852, 2101, 1677, 1642, 1513 cm^{-1}.

(1*S*,2*R*)-2-(prop-2-ynylcarbamoyl)cyclobutanaminium trifluoroacetate (11): Compound **10** (0.03 g, 0.12 mmol, 1 eq) was dissolved in DCM (2.4 mL). TFA (1.32 mL, 17.25 mmol, 145 eq) was slowly added. The mixture was stirred for 15 min at room temperature until the entire reagent reacted (monitored by TLC). Subsequently, the solvent and TFA were evaporated. Compound **11** was obtained in form of a yellow oil and used in the following reaction without further purification (0.018 g, 0.12 mmol, 99% yield). ^{1}H-NMR (250 MHz, $CDCl_3$) δ 2.11–2.66 (m, 5H), 3.23–3.48 (m, 1H), 3.92–4.30 (m, 3H), 7.99 (br. s, 1H), 9.31 (br. s, 1H).

Benzyl (1*S*,2*R*)-2-(prop-2-ynylcarbamoyl)cyclobutylcarbamate (12): A flask containing acid 1[7a] (0.28 g, 1.12 mmol, 1.0 eq) and *N,N'*-dicyclohexylcarbodiimide (DCC) (0.25 g, 1.24 mmol, 1.1 eq) was deoxygenized with nitrogen. Anhydrous DCM (12 mL) was added. After the solid was dissolved, propargyl amine (0.08 mL, 1.24 mmol, 1.1 eq) was injected and the reaction mixture stirred for 18 h. Subsequently, the solvent was evaporated and the yellow residue was purified by column chromatography from hexane:EtOAc (1:10, R_f=0.57). Compound **12** was obtained in form of a white solid (0.17 g, 0.58 mmol, 52% yield). $[\alpha]_D$: −76.7 (c 1, DCM). m.p. 148–152 °C (EtOAc). ^{1}H-NMR (250 MHz, $CDCl_3$) δ 1.83–2.60 (m, 5H), 3.16–3.37 (m, 1H), 3.86–4.10 (m, 2H), 4.49 (m, 1H), 5.01–5.27 (m, 2H), 5.73 (br. d, $^3J_{H-H}$=7.7 Hz, 1H), 6.01 (br. s, 1H), 7.14–7.63 (m, 5H). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ 17.9, 28.1, 28.8, 45.9, 46.4, 66.5, 71.2, 79.2, 127.8, 127.9, 128.3, 136.1, 155.6, 172.2. HRMS (ESI): $C_{16}H_{18}N_2NaO_3$ requires 309.1210, found $[M+Na]^+$309.1211. IR (ATR) 3341, 3319, 3257, 3063, 3040, 3012, 2960, 2945, 2120, 1676, 1643, 1533, 1520 cm^{-1}.

Functionalized peptide (13): Compound **8** (0.14 g, 0.44 mmol, 1.0 eq) and FDPP (0.19 g, 0.50 mmol, 1.1 eq) were deoxygenized with N_2 in a round-bottomed flask. 20 mL of anhydrous DCM and DIPEA (0.32 mL, 1.85 mmol, 4.2 eq) were added and the mixture stirred for 5 min. After, compound **7** (0.07 g, 0.44 mmol, 1.0 eq) dissolved in DMF (1.1 mL) was injected and the mixture was stirred for 20 h at room temperature. Subsequently, the solvent was evaporated, and a yellow solid was obtained. The residue was lyophilized to remove DMF. EtOAc (20 mL) was added to the solid and the solution was washed with sat. $NaHCO_{3(aq)}$ (20 mL) and water (20 mL). The aqueous layer was reextracted with EtOAc and the combined organic layers dried over $MgSO_4$, filtered and the solvent was evaporated. The residue was lyophilized again to remove traces of DMF. The yellowish solid was suspended in a small quantity of Et_2O at 0 °C and stirred vigorously for 30 min. After the suspension settled, the solvent was decanted, and the procedure repeated additional two times. Compound **13** was purified by column chromatography from EtOAc:MeOH (10:1, R_f=0.19). Additionally, the product was recrystallized from a 0.02 g/mL DCM solution by diffusion of Et_2O at 4 °C for 48 h and obtained as a white solid (0.04 g, 0.09 mmol, 20% yield). $[\alpha]_D$: −101.1 (c 1, MeOH). m.p. 150–153 °C (acetone). ^{1}H-NMR (250 MHz, CD_3OD) δ 1.87–2.13 (m, 4H), 2.13–2.42 (m, 4H), 3.19–3.46 (m, 5H) 3.51–3.69 (m, 2H), 3.69–3.74 (m, 1H), 3.79–3.94 (m, 1H), 4.47 (m, 1H), 4.58 (m, 1H), 4.97–5.24 (m, 2H), 7.26–7.42 (m, 5H). ^{13}C-NMR (62.5 MHz, CD_3OD) δ 17.2, 17.9, 27.3, 27.9, 41.3, 41.7, 45.0, 45.5, 46.3, 46.8, 60.1, 65.8, 127.1, 127.3, 127.8, 136.6, 156.2, 169.6, 173.5, 173.6. HRMS (ESI): $C_{22}H_{30}N_4NaO_6$ requires 469.2063, found $[M+Na]^+$469.2069. IR (ATR) 3388, 2949, 2413, 1700, 1634, 1453, 1338, 1237 cm^{-1}.

Functionalized peptide (14): Compound **8** (47 mg, 0.15 mmol, 1.2 eq) and FDPP (56 mg, 0.14 mmol, 1.1 eq) were deoxygenized with N_2 in a round-bottomed flask. Anhydrous DCM (2 mL) and DIPEA (0.14 mL, 0.79 mmol, 6.0 eq) were added and the mixture stirred for 5 min. After, compound **11** (20 mg, 0.13 mmol, 1.0 eq) was dissolved in anhydrous DCM (2 mL) and added to the mixture, which was stirred for 16 h at room temperature. Subsequently, the solvent was evaporated, and a yellow solid was obtained. The residue was suspended in water. The aqueous layer was extracted with DCM (3×10 mL) and the combined organic layers dried over $MgSO_4$, filtered and the solvent was evaporated. The yellow solid was purified by column chromatography from EtOAc: MeOH (10:1, R_f=0.53). Compound **14** was obtained in the form of a white solid (32 mg, 0.07 mmol, 46% yield). $[\alpha]_D$: −148.9 (c 1.2, MeOH). m.p. 1st transition 160–165 °C; 2nd transition 172–174 °C (MeOH). ^{1}H-NMR (250 MHz, CD_3OD) δ 1.82–2.46 (m, 8H), 2.56–2.62 (m, 1H), 3.18–3.48 (m, 4H), 3.60–4.05 (m, 4H), 4.37–4.68 (m, 2H), 4.97–5.20 (m, 2H), 7.17–7.44 (m, 5H). ^{13}C-NMR (62.5 MHz, CD_3OD) δ 17.2, 17.8, 27.3, 27.7, 41.8, 44.8, 44.9, 45.4, 46.4, 65.8, 70.4, 79.3, 127.2, 127.4, 127.8, 136.6, 156.2, 169.3, 172.9, 173.6. HRMS (ESI): $C_{23}H_{28}N_4NaO_5$ requires 463.1952, found $[M+Na]^+$463.1948. IR (ATR) 3296, 2950, 2468, 1684, 1633, 1538, 1430 cm^{-1}.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Amino acids · Chiral scaffolds · Peptidomimetics · Polyfuctional chemical platforms · Unnatural peptides

[1] S. Hanessian. Total Synthesis of Natural Products: The "Chiron" Approach. Pergamon Press Ltd. 1983.
[2] P. Singh, K. Samanta, S. K. Das, G. Panda, *Org. Biomol. Chem.* **2014**, *12*, 6297–6339.
[3] S. M. Paek, M. Jeong, J. Jo, Y. M. Heo, Y. T. Han, Y. Yun, *Molecules* **2016**, *21*, 951.
[4] P. Hughes, J. Clardy, *J. Org. Chem.* **1988**, *53*, 4793–4796.
[5] A. Avenoza, J. H. Busto, N. Canal, F. Corzana, J. M. Peregrina, M. Pérez-Fernández, F. Rodriguez, *J. Org. Chem.* **2010**, *75*, 545–552.
[6] a) C. Fernandes, C. Gauzy, Y. Yang, O. Roy, E. Pereira, S. Phaure, D. J. Aitken, *Synthesis* **2007**, *14*, 2222–2232 ; b) C. Fernandes, E. Pereira, S. Phaure, D. J. Aitken, *J. Org. Chem.* **2009**, *74*, 3217–3220.

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[7] a) M. Martín-Vilà, E. Muray, G. P. Aguado, Á. Álvarez-Larena, V. Branchadell, C. Minguillón, E. Giralt, R. M. Ortuño, *Tetrahedron: Asymmetry* **2000**, *11*, 3569–3584; b) S. Izquierdo, F. Rúa, A. Sbai, T. Parella, V. Branchadell, R. M. Ortuño, *J. Org. Chem.* **2005**, *70*, 7963–7971.
[8] V. André, A. Vidal, J. Ollivier, S. Robin, D. J. Aitken, *Tetrahedron Lett.* **2011**, *52*, 1253–1255.
[9] J. Aguilera, J. A. Cobos, R. Gutierrez-Abad, C. Acosta, P. Nolis, O. Illa, R. M. Ortuno, *Eur. J. Org. Chem.* **2013**, *17*, 3494–3503.
[10] H. Awada, C. M. Grison, F. Charnay-Pouget, J.-P. Baltaze, F. Brisset, R. Guillot, S. Robin, A. Hachem, N. Jaber, D. Naoufal, O. Yazbeck, D. J. Aitken, *J. Org. Chem.* **2017**, *82*, 4819–4828.
[11] S. Kerres, E. Plut, S. Malcherek, J. Rehbein, O. Reiser, *Adv. Synth. Catal.* **2019**, *361*, 1400–1407.
[12] R. M. Ortuño, *Gels* **2021**, *7*, 54.
[13] O. Illa, O. Porcar-Tost, C. Robledillo, C. Elvira, P. Nolis, V. Branchadell, O. Reiser, R. M. Ortuño, *J. Org. Chem.* **2018**, *83*, 350–363.
[14] O. Porcar-Tost, B. Pi-Boleda, J. García-Anton, O. Illa, R. M. Ortuño, *Tetrahedron* **2018**, *74*, 7252–7260.
[15] E. Gorrea, E. Torres, P. Nolis, E. Da Silva, D. B. Amabilino, V. Branchadell, R. M. Ortuño, *Chem. Eur. J.* **2011**, *17*, 4588–4597.
[16] S. Celis, P. Nolis, V. Branchadell, O. Illa, R. M. Ortuño, *Org. Biomol. Chem.* **2013**, *11*, 2839–2846.
[17] E. Torres, L. Puigmartí-Luis, Á. Pérez del Pino, R. M. Ortuño, D. B. Amabilino, *Org. Biomol. Chem.* **2010**, *8*, 1661–1665.
[18] O. Illa, J. Ospina, J.-E. Sánchez-Aparicio, X. Pulido, M. Á. Abengozar, N. Gaztelumendi, D. Carbajo, C. Nogués, L. Rivas, J.-D. Maréchal, M. Royo, R. M. Ortuño, *Int. J. Mol. Sci.* **2021**, *22*, 5092.
[19] A. A. Balasubramaniam, *Peptides* **1997**, *18*, 445–457.
[20] L. Beelicki, M. Kaske, R. Gutiérrez-Abad, G. Reinhardt, O. Illa, R. M. Ortuño, C. Cabrele, A. Buschauer, O. Reiser, *J. Med. Chem.* **2013**, *56*, 8422–8431.
[21] B. Pi-Boleda, S. Ramissety, O. Illa, V. Branchadell, R. S. Dias, R. M. Ortuño, *ACS Appl. Biomat.* **2021**, *4*, 7034–7043.
[22] a) W. Mansawat, C. Vilaivan, Á. Balázs, D. J. Aitken, T. Vilaivan, *Org. Lett.* **2012**, *14*, 1440–1443; b) B. Ditmanklo, W. Sittiwong, T. Boddaert, C. Vilaivan, D. J. Aitken, *Biopolymers* **2021**, *112*, DOI: 10.1002/bip.23459.
[23] P. E. Nielsen, M. Egholm, R. H. Berg, *Science* **1991**, *254*, 1497.
[24] a) Z. Chang, F. Boyaud, R. Guillot, T. Boddaert, D. J. Aitken, *J. Org. Chem.* **2018**, *83*, 627–534; b) Z. Chang, F. Boyaud, R. Guillot, T. Boddaert, D. J. Aitken, *J. Org. Chem.* **2019**, *84*, 10518–10525.
[25] M. El Haimer, M. Palkó, M. Haukka, M. Gajdács, I. Zupkó, F. Fülöp, *RSC Adv.* **2021**, *11*, 6952–6957.
[26] J. A. Marchand, M. E. Neugebauer, M. C. Ing, C.-I. Lin, J. G. Pelton, M. C. Y. Chang, *Nature* **2019**, *567*, 420–424.
[27] D. Fernández, E. Torres, F. X. Avilés, R. M. Ortuño, J. Vendrell, *Bioorg. Med. Chem.* **2009**, *17*, 3824–3828.
[28] S. Celis, E. Gorrea, P. Nolis, O. Illa, R. M. Ortuño, *Org. Biomol. Chem.* **2012**, *10*, 861–868.
[29] a) S. Ohira, *Synth. Commun.* **1989**, *19*, 561–564; b) S. Müller, B. Liepold, G. J. Roth, H. J. Bestmann, *Synlett* **1996**, *1996*, 521–522.
[30] G. J. Roth, B. Liepold, S. G. Müller, H. J. Bestmann, *Synthesis* **2004**, *2004*, 59–62.

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