Monatsh Chem
https://doi.org/10.1007/s00706-017-2126-2

ORIGINAL PAPER

Peptide-catalyzed stereoselective Michael addition of aldehydes and ketones to heterocyclic nitroalkenes

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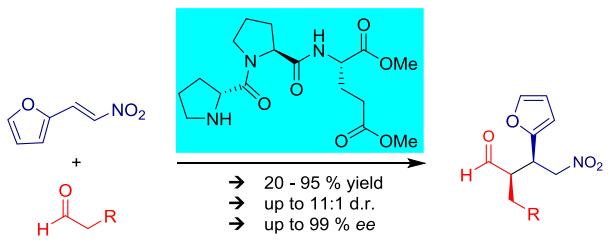
Received: 8 November 2017 / Accepted: 3 December 2017

Abstract Stereoselective Michael addition of enolizable carbonyl compounds to a furane-derived nitroalkene was catalyzed by di- and tripeptide organocatalysts. The most competent catalysts were tripeptides possessing Pro–Pro–Glu structure. With aldehydes, Michael adducts were obtained in high yields and with medium-to-high diastereo- (up to 13:1 d.r.) and enantiomeric purities (up to 99% *ee*). The reaction was less stereoselective with cyclic ketones than with aldehydes.

Graphical abstract



Keywords Catalysis · Peptides · Michael addition · Carbonyl compounds · Heterocycles

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Introduction

Heterocyclic compounds, including chiral ones, are broadly distributed in nature [1]. Heteroaromatics, as well as saturated heterocycles, belong among the most important pharmacophores [2]. Asymmetric organocatalysis gives access to numerous chiral heterocyclic compounds [3–5]. Michael addition is one of the principal C–C bond building strategies [6–8].

Short-chain peptides have found many uses in asymmetric catalysis [9–12]. Peptides proved valuable alternatives to enzymes for modifications of complex natural products [13]. Seminal Miller's discoveries of nucleophilic peptide-based catalysts for acylations [14] and later on phosphorylations [15, 16] and sulfinylations [17] stimulated the interest of the organic chemistry community in catalytic peptides. Short-chain peptides or peptide-based catalysts can also catalyze many other reactions. Peptides possessing a free primary or secondary amine group can activate enolizable carbonyl compounds via enamine formation. In this way, peptides served as catalysts for numerous aldol-type reactions [18–28]. Similarly, peptides engage in several Michael additions. In 2006, Cordova and co-workers showed that di- and tripeptides can catalyze Michael addition of ketones to nitroalkenes [29]. Wennemers et al. developed N-terminal proline tripeptides as excellent catalysts for 1,4-additions of aldehydes to nitroalkenes [30–36]. These type of catalysts proved robust enough even for immobilization on solid supports [37, 38]. Peptide catalysts found use also in 1,4-additions to other types of Michael acceptors, such as maleimides [39] or enals [40, 41]. In addition, modified peptides, such as diketopiperazines, dipeptide-derived phosphonium salts, and tetrahydropyran-based dipeptides, are competent catalysts for Michael additions [42–44]. The catalytic activity

Published online: 15 December 2017

of peptides is closely linked with their secondary structures [45, 46].

Although large attention has already been focused on organocatalytic Michael additions, substrates containing heterocyclic moieties were studied only sparingly. Given the importance and widespread occurrence of the heterocyclic skeleton in biologically active compounds, we have decided to investigate Michael addition of carbonyl compounds to heterocyclic nitroalkenes. In this paper, we present the results of our studies of asymmetric 1,4-additions of aldehydes and ketones to heterocyclic nitroalkenes catalyzed by short-chain peptides.

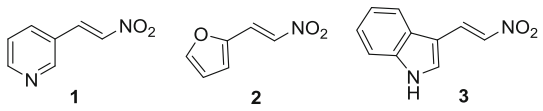
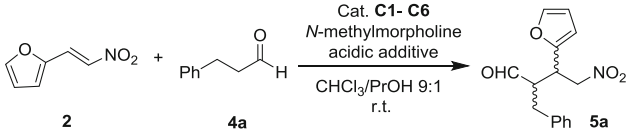


Fig. 2 Heterocyclic nitroalkenes used in this study

Scheme 1



Results and discussion

We have started our investigation by synthesis of peptides. Using the literature procedures, we have synthesized six short-chain peptides containing N-terminal proline residue (Fig. 1). This proline moiety is important for the supposed enamine-forming activity of catalysts. Catalyst **C1** is composed of two L-proline moieties. Catalysts **C2** and **C3** contain D-proline and a glutamic acid having both protected and free carboxylic functions. Catalyst **C4** is a tripeptide comprising L-Pro-L-Pro-L-Glu. Catalysts **C5** and **C6** possess D-Pro-L-Pro motive combined with either protected or unprotected glutamic acid. Glutamic acid can act as an additional Bronsted acid, which can accelerate Michael additions. This idea has been suggested by Wennemers for similar peptides containing either aspartic or glutamic acid [30, 38].

With peptidic catalysts in hands, we started to investigate Michael additions to heterocyclic nitroalkenes **1**–**3** (Fig. 2). Pyridine-based nitroalkene **1** was commercially available. Furane derivative **2** and indol-derived alkene **3** were synthesized by the nitro-aldol reaction between corresponding aldehydes and nitromethane [47].

Nitroalkenes **1** and **3** proved to be unreactive in Michael additions of enolizable aldehydes. Despite several attempts under various conditions, we were not able to isolate corresponding Michael adducts using none of peptidic catalysts. On the other hand, furane-derived nitroalkene **2** afforded corresponding Michael adduct **5a** in the reaction with 3-phenylpropanal (**4a**) (Scheme 1).

We have screened peptide catalysts **C1**–**C6** in the Michael reaction of phenylpropanal (**4a**) with nitroalkene **2**. Interestingly, all catalysts afforded product **5a** in good yield and medium-to-high diastereomeric and enantiomeric purity. The best performance was achieved by tripeptide catalysts **C5** and **C6** (Table 1, entries 10 and 11). Table 1 summarizes the results of catalysts screening in the reaction of nitroalkene **2** with 3-phenylpropanal (**4a**).

We have also tested Michael additions of a series of aliphatic aldehydes **4b**–**4e** to nitroalkene **2** (Scheme 2). Corresponding Michael adducts **5b**–**5e** were isolated in good yields but with compromised diastereomeric and enantiomeric purities.

With nitroalkene **2**, we have also explored Michael additions of cyclic ketones, cyclopentanone (**6a**) and cyclohexanone (**6b**) (Scheme 3). Corresponding Michael adducts **7a**, **7b** were obtained in good yields but in only

Fig. 1 Peptidic organocatalysts used in this study

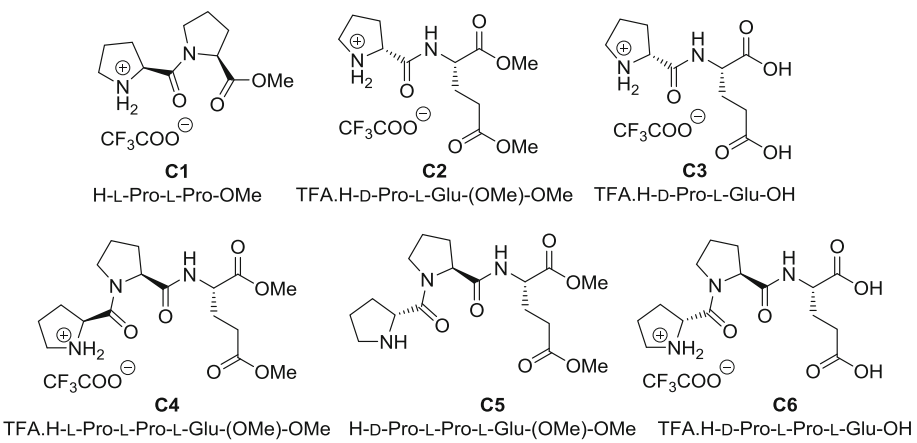


Table 1 Screening of peptide catalysts in the Michael reaction of 3-phenylpropanal (**4d**) with nitroalkene **2**

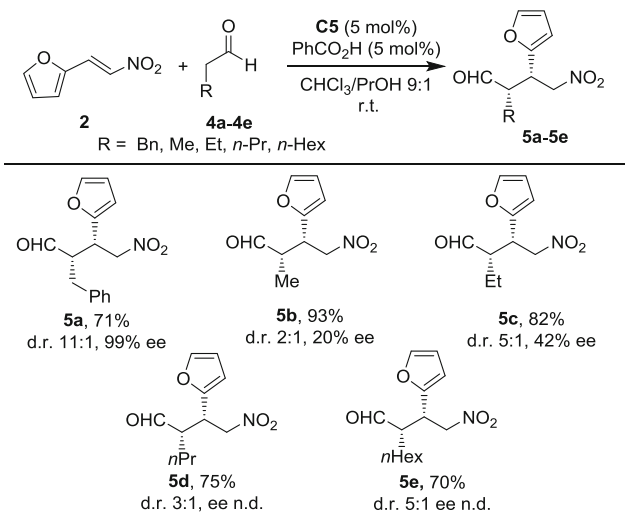
Entry	Catalyst	Additive/loading/mol%[a]	Time/h	Yield/%	d.r. (syn:anti)	*ee*/%[c]
1	H-L-Pro-L-Pro-OMe (TFA.**C1**)	–/10	18	93	3:1	84 (*R,S*)
2	H-L-Pro-L-Pro-L-Glu(OMe)-OMe (TFA.**C4**)	–/1	72	20	5:1	96 (*R,S*)
3	H-L-Pro-L-Pro-L-Glu(OMe)-OMe (TFA.**C4**)	–/3	36	67	5:1	99 (*R,S*)
4	H-L-Pro-L-Pro-L-Glu(OMe)-OMe (TFA.**C4**)	$PhCO_2H$/3	24	95	5:1	99 (*R,S*)
5	H-L-Pro-L-Pro-L-Glu(OMe)-OMe (TFA.**C4**)	AcOH/3	24	95	4:1	99 (*R,S*)
6	H-L-Pro-L-Pro-L-Glu(OMe)-OMe (TFA.**C4**)	(*R*)-mandelic a./3	24	93	4:1	67 (*R,S*)
7	H-D-Pro-L-Glu-OH (TFA.**C3**)[b]	–/5	72	61	13:1	99 (*S,R*)
8	H-D-Pro-L-Glu(OMe)-OMe (TFA.**C2**)[b]	–/5	72	69	9:1	99 (*S,R*)
9	H-D-Pro-L-Pro-L-Glu(OMe)-OMe (**C5**)	–/5	36	71	11:1	99 (*S,R*)
10	H-D-Pro-L-Pro-L-Glu-OH (TFA.**C6**)	–/5	36	69	13:1	> 99 (*S,R*)

[a]Loading of catalyst, NMM, as well as acidic additive

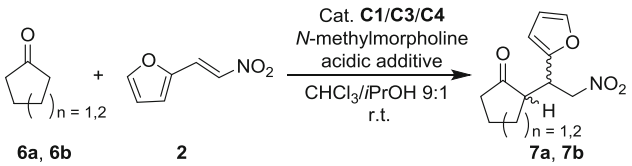
[b]Solvent $CHCl_3$/*i*-PrOH 1:1

[c]Enantiomeric excesses determined by chiral HPLC; absolute configuration assigned by analogy with the literature [30]

Scheme 2



Scheme 3



medium or low enantiomeric purity. The results of Michael addition of cyclic ketones with nitroalkene **2** are summarized in Table 2.

To gain insight into catalytic activities, we have calculated geometries of three most effective catalysts **C3**, **C5**, and **C6**. DFT calculation at ωB97X-D/6-31G* level showed that all catalysts display typical hairpin structure supported by intramolecular hydrogen bonds. Catalysts **C3** and **C5**, which comprise D-Pro-L-Pro arrangement, have hydrogen bond between N-terminal proline moiety and glutamic acid (**C3**: N—HOOC; **C5**: NH—O=C). On the other hand, catalyst **C6** shows hydrogen bonding between amide NH of glutamic acid and nitrogen of terminal proline moiety (Fig. 3).

Conclusion

Short-chain peptide organocatalysts possessing N-terminal proline moiety are effective catalysts for Michael additions of aldehydes to furan-derived nitroalkene. The corresponding Michael adducts were obtained in high yields (70–93%). The Michael addition of 3-phenylpropanal also proceeded with high diastereo- and enantioselectivity (13:1 d.r., 99% *ee*), but aliphatic aldehydes reacted with only moderate stereoselectivities. Peptidic catalysts were less efficient in 1,4-additions of cyclic ketones.

Experimental

All chemicals and solvents were purchased from Alfa Aesar or Sigma-Aldrich. All reactions were performed under an Ar-atmosphere. The solvents were purified and dried according to the standard techniques. Thin-layer chromatography was performed on Merck TLC-plates silica gel 60, F-254, or on Al_2O_3 TLC-plates. Compounds were visualized by irradiation with UV light and/or by treatment with solutions of $KMnO_4$ or ninhydrin reagent. Products Michael additions from reaction mixtures were

Table 2 Michael addition of cyclic ketones to nitroalkene **2**

Entry	Ketone	Catalyst	Catalyst loading/mol%[a]	Time/h	Yield/%	d.r. (syn/anti)	*ee*/%[c]
1	**6a**	**C3**	5	72	31	4:1	19 (*S*,*S*)
1	**6b**	**C1**	10	18	83	6:1	26 (*R*,*R*)
2	**6b**	**C4**	5	24	95	10:1	36 (*R*,*R*)
3	**6b**	**C4**[b]	3	72	45	6:1	9 (*R*,*R*)
4	**6b**	**C3**	5	120	20	7:1	16 (*S*,*S*)

[a]Catalyst as well as NMM loading

[b]$PhCO_2H$ (3 mol %) as additive

[c]Enantiomeric excesses determined by chiral HPLC; absolute configuration assigned by comparison of the sign of optical rotation with the literature data [48]

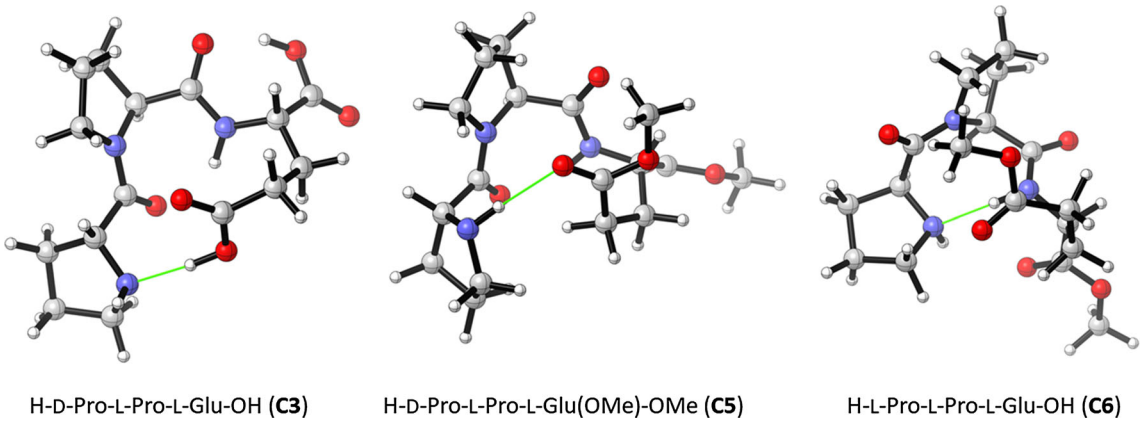


Fig. 3 Lowest energy conformers of catalysts **C3**, **C5**, and **C6** calculated at ωB97X-D/6-31G* level

after general work-up separated by flash chromatography using Isolera Biotage FSKO-1107-0010. NMR spectra were recorded on Varian NMR System 300 (300 or 600 MHz for ^{1}H and 75 MHz for ^{13}C). Chemical shifts (δ) are given in ppm relative to tetramethylsilane. Melting points were measured on an M-656 Büchi. High-resolution mass spectra (HRMS) were recorded on Orbitrap Elite Thermo Scientific Velos Pro, ionization mode: HESI heated electrospray. Enantiomeric excesses were determined by chiral HPLC using Diacel Chiralcel OD-H, AD-H, AS-H columns with isopropyl alcohol and hexane or heptane as the eluents. Optical rotations were recorded on Jasco P-2000 polarimeter.

Syntheses of peptidic catalysts

Peptides prepared by solution phase synthesis. The syntheses of peptide catalysts were carried out according to the standard methods of solution phase synthesis of peptides [36, 49–52].

N-Boc-D-Pro-L-Pro-OMe

N-Boc-D-Pro-OH (600 mg, 2.8 mmol), 639 mg EDC·HCl (3.3 mmol), and 512 mg HOBt·H_2O (3.3 mmol) were suspended in 10 cm^3 dry CH_2Cl_2 and cooled an ice bath under a nitrogen atmosphere. DIPEA (*i*PrNEt$_2$) (1.07 cm^3) was added dropwise over 10 min, and the resulting yellow solution was stirred for an additional 10 min, and then added 462 mg HCl·H-L-Pro-OMe (2.8 mmol) as a solid. The resulting homogeneous yellow reaction mixture was stirred at room temperature for 10 h and diluted with 15 cm^3 of 0.1 M HCl. The layers were separated, and the aqueous phase extracted with EtOAc (3 × 10 cm^3). The combined organic phases were washed with 15 cm^3 1 M $NaHCO_3$ solution, 15 cm^3 water, and 15 cm^3 brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography and visualized with ninhydrin to afford the title compound. *N*-Cbz-protecting peptides were prepared in analogously using *N*-Cbz-D-Pro-OH.

N-Boc-D-Pro-L-Pro-OMe

It was observed as a mixture of conformers (77%), as a clear colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.00–4.35 (m, 2H), 3.80–3.35 (m, 7H), 2.41–1.74 (m, 8H), 1.47–1.40 (4 × s, 9H) ppm. Spectral data agree with those in the literature [36].

N-Boc-L-Pro-L-Pro-OMe

It was observed as a mixture of conformers, as a clear colorless oil (87%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.61–4.37$ (m, 2H), 3.80–3.35 (m, 7H), 2.23–1.83 (m, 8H), 1.45 and 1.39 (2 × s, 9H) ppm. Spectral data agree with those in the literature [53].

N-Boc-D-Pro-L-Glu(OMe)-OMe

It was obtained as a white powder (86%). M.p.: 55–57 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.73$ (s, 1H), 4.62 (td, d, $J = 8.1$, 5.1 Hz, 1H), 4.29 (s, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 3.46 (m, 2H), 3.49 (m, 2H), 2.50–1.85 (m, 8H), 1.47 (s, 9H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 173.2$, 172.2, 155.9, 154.7, 129.1, 128.9, 125.4, 125.2, 120.4, 120.3, 109.5, 105.1, 85.2, 80.7, 61.3, 60.2, 52.6, 51.9, 51.5, 47.2, 31.2, 29.9, 28.5, 27.5, 24.6, 23.8 ppm; HRMS: *m/z* calculated for $C_{17}H_{29}N_2O_7$ $[M + H]^+$ 373.1969, found 373.1968; for Na-adduct calc. for $C_{17}H_{28}N_2NaO_7$ $[M + Na]^+$ 395.1789, found 395.1788.

N-Cbz-D-Pro-L-Pro-OMe

It was observed as a mixture of rotamers (77%), as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.47–7.27$ (m, 5H), 5.29–4.88 (m, 2H), 4.65–4.38 (m, 1H), 4.32–4.08 (m, 1H), 3.81–3.28 (m, 7H), 2.43–1.76 (m, 8H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 173.6$, 173.1, 172.7, 172.8, 172.6, 172.5, 171.8, 171.8, 155.4, 155.1, 154.7, 154.3, 137.4, 137.3, 137.0, 136.7, 129.1, 129.0, 128.9, 128.8, 128.6, 128.3, 128.2, 128.2, 128.1, 67.9, 67.4, 67.3, 67.3, 59.8, 59.7, 59.7, 59.5, 58.6, 58.3, 58.3, 57.7, 52.9, 52.6, 52.5, 47.9, 47.5, 47.4, 47.2, 47.1, 47.0, 34.4, 31.8, 31.4, 31.2, 30.9, 30.4, 29.9, 29.4, 29.3, 26.5, 26.4, 26.1, 26.0, 25.8, 25.4, 25.3, 25.2, 25.1, 24.7, 24.3, 23.9, 23.1, 22.7 ppm; IR (ATR): $\bar{\nu} = 3319$, 2950, 2929, 2878, 2205, 2110, 1879, 1741, 1701, 1653, 1577, 1541, 1498, 1411, 1351, 1323, 1270, 1242, 1194, 1323, 1270, 1242, 1194, 1167, 1114, 1086, 1046, 986, 965, 917, 891, 766, 739, 698 cm^{-1}; HRMS: *m/z* calculated for $C_{19}H_{25}N_2O_5$ $[M + H]^+$ 361.1758, found 361.1759; Na-adduct calculated for $C_{19}H_{24}N_2NaO_5$ $[M + Na]^+$ 383.1577, found 383.1580; $[\alpha]_D^{20} = -3.5$ ($c = 1$, MeOH).

N-Cbz-D-Pro-L-Pro-L-Glu(OMe)-OMe

It was obtained as a colorless oil (64%). ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 7.66$ (d, $J = 8.2$ Hz, 1H), 7.35–7.31 (m, 5H), 5.15 (d, $J = 12.5$ Hz, 1H), 5.00 (d, $J = 12.5$ Hz, 1H), 4.71 (d, $J = 8.0$ Hz, 1H), 4.47 (m, 2H), 3.99 (m, 1H), 3.67 (s, 3H), 3.62 (s, 3H), 3.56 (m, 1H), 2.46–1.85 (m, 14 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 173.5$, 173.3, 172.1, 171.9, 171.6, 155.4, 136.8, 129.1, 129.0, 128.9, 128.8, 128.7, 128.7, 128.3, 128.2, 127.9, 125.5, 125.2, 120.5, 120.4, 109.6, 109.6, 85.3, 67.3, 60.6, 58.2, 52.4, 52.0, 51.8, 47.4,47.1, 30.6, 30.1, 30.0, 29.9, 29.4, 28.8, 27.5, 27.3, 26.7, 25.1, 24.4 ppm; MS (ESI): *m/z* calculated for $C_{25}H_{33}N_3O_8$ $[M + H]^+$ 504.23, found 504.2; Na-adduct calculated for $C_{25}H_{33}N_3O_8$ $[M + Na]^+$ 526.2, found 526.2.

N-Boc-D-Pro-L-Pro-L-Glu(OMe)-OMe

It was obtained as a colorless oil (61%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.71–4.74$ (m, 1H), 4.48–4.39 (m, 2H), 3.93–3.40 (m, 10H), 2.49–1.82 (m, 12H), 1.42 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 173.0$, 172.2, 171.6, 171.5, 79.7, 60.1, 57.8, 52.1, 52.0, 51.5, 47.1, 46.9, 30.5, 29.2, 28.3, 28.1, 26.3, 24.6, 24.3 ppm.

N-Boc-L-Pro-L-Pro-L-Glu(OMe)-OMe

It was observed as a mixture of conformers (64%), as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.64–4.33$ (m, 3H), 3.75–3.42 (m, 9H), 2.61–1.66 (m, 12H), 1.42 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 173.2$, 172.9, 172.7, 172.1, 171.9, 171.8, 171.5, 171.4, 171.0, 154.5, 80.0, 79.6, 60.9, 59.8, 58.0, 57.7, 57.6, 52.4, 52.1, 51.7, 51.5, 47.1, 46.9, 46.7, 31.4, 30.8, 29.9, 29.5, 29.3, 28.5, 28.4, 27.4, 27.1, 25.3, 24.7, 24.7, 24.1, 23.5, 22.2 ppm; MM-ES + APCI: *m/z* calculated for $C_{22}H_{35}N_3NaO_8$ Na-adduct $[M + Na]^+$ 492.2316, found 492.2318; $[\alpha]_D^{20} = -108$ ($c = 1$, MeOH).

General procedure for deprotection of the carboxyl group

To a solution of 130 mg *N*-Boc-D-Pro-L-Glu(OMe)-OMe (0.28 mmol) in 3 cm^3 MeOH was added 0.7 cm^3 1 M NaOH and the resulting solution was stirred at room temperature 2 h. The reaction mixture was concentrated under reduced pressure, and the resulting aqueous phase was acidified to pH 1 with conc. HCl and extracted with CH_2Cl_2 (3 × 7 cm^3). The combined organic layers were washed with brine and dried over Na_2SO_4, and the solvent was removed under reduced pressure to afford the title compound.

N-Boc-D-Pro-L-Glu(OH)-OH

It was obtained as a colorless oil (53%). ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 10.7$ (br s, 2H), 4.49 (m, 1H), 4.31 (m, 1H), 3.52–3.43 (m, 2H), 2.50–1.87 (m, 8H), 1.41 (s, 9H) ppm; MS (ESI): *m/z* calculated for Na-adduct $C_{15}H_{24}N_2NaO_7$ $[M + Na]^+$ 367.1, found 367.1.

N-Boc-D-Pro-L-Pro-OH

It was obtained as a mixture of rotamers (87%), as a white solid. M.p.: 191–192 °C recrystallized from ethyl acetate (196–197 °C [54]); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 11.6$ (br s, 1H), 4.65–4.62 (m, 1H), 4.47–4.42 (m, 1H), 3.79–3.42 (m, 4H), 2.62–1.85 (m, 8H), 1.44 and 1.40 (s, 9H) ppm. Spectral data agree with those in the literature [36].

N-Boc-L-Pro-L-Pro-OH
It was obtained as a mixture of conformers (86%), as a white solid. M.p.: 177–181 °C recrystallized from EtOAc (177–180 °C [55]); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.71$–4.60 (m, 1H), 4.53–4.38 (m, 1H), 3.84–3.38 (m, 4H), 2.54–1.85 (m, 8H), 1.43 and 1.40 (s, 9H) ppm. Spectral data agree with those in the literature [53]. $[\alpha]_D^{20} = -150$ ($c = 1$, MeOH) [55].

N-Boc-D-Pro-L-Pro-L-Glu(OH)-OH
It was obtained as a colorless oil (78%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.81$ (bs, 2H), 4.67–4.35 (m, 3H), 3.96–3.36 (m, 4H), 2.43–1.80 (m, 12H), 1.42 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 176.0$, 175.9, 175.7, 173.4, 173.2, 173.0, 172.2, 172.0, 171.7, 80.8, 80.5, 80.4, 80.1, 60.8, 58.4, 58.1, 57.9, 53.5, 52.6, 52.3, 51.7, 47.3, 47.2, 30.7, 30.3, 29.7, 29.3, 28.8, 28.5, 28.2, 26.0, 24.7, 24.6, 24.4, 23.5 ppm.

N-Cbz-D-Pro-L-Pro-OH
It was obtained as a mixture of conformers (91%), as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 10.76$ (s, 1H), 7.42–7.27 (m, 5H), 5.15–4.88 (m, 2H), 4.58–3.98 (m, 2H), 3.63–3.29 (m, 4H), 2.39–1.65 (m, 8H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 174.8$, 174.6, 174.0, 173.3, 172.9, 172.8, 172.5, 172.3, 155.1, 155.1, 154.1, 154.0, 136.5, 136.4, 136.2, 128.6, 128.6, 128.5, 128.5, 128.4, 128.4, 128.3, 128.3, 128.1, 128.0, 127.9, 127.6, 120.2, 120.1, 67.6, 67.3, 67.1, 60.2, 59.4, 59.1, 58.3, 58.0, 57.8, 57.4, 53.5, 47.6, 47.4, 47.2, 47.1, 47.1, 46.9, 46.8, 46.7, 31.4, 31.1, 30.7, 30.3, 30.0, 29.3, 28.2, 27.6, 24.7, 24.6, 24.5, 24.5, 23.9, 23.8, 22.5, 22.2 ppm; IR (ATR): $\bar{\nu} = 2956$, 2879, 2514, 1877, 1701, 1654, 1608, 1412, 1351, 1266, 1168, 1116, 1116, 1087, 913, 874, 824, 767, 730 cm^{-1}.

General procedure for deprotection Boc-protecting group

To 222 mg of the *N*-Boc-L-Pro-L-Pro-L-Glu(OMe)-OMe (0.47 mmol) in 5 cm^3 CH_2Cl_2 was added 0.6 cm^3 TFA. The solution was kept at room temperature for 2 h and the TFA evaporated to dryness. The oily residue was evaporated with toluene three times and washed with a solution of Et_2O/hexane (1:2) to afford the title compound.

TFA.H-L-Pro-L-Pro-L-Glu(OMe)-OMe (**C4**)
It was obtained as a pale brown oil (91%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 11.56$ (s, 1H), 9.96 (s, 1H), 4.81–4.70 (m, 1H), 4.58–4.45 (m, 2H), 3.76–3.36 (m, 10H), 2.60–1.97 (m, 12H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 173.2$, 171.8, 171.6, 167.7, 160.9 (q, $J = 38.8$ Hz), 115.64 (q, $J = 288.0$ Hz), 60.6, 58.6, 52.5, 51.83, 51.82, 47.5, 47.1, 29.9, 29.0, 28.7, 27.0, 24.9, 24.6 ppm; IR (ATR): $\bar{\nu} = 3323$, 3072, 2958, 2713, 2437, 2331, 2114, 1989, 1735, 1649, 1542, 1439, 1371, 1343, 1164, 984, 916, 797, 722 cm^{-1}; HRMS: *m/z* calculated for $C_{17}H_{28}N_3O_6$ $[M + H]^+$ 370.1973, found 370.1977; $[\alpha]_D^{20} = -0.6$ ($c = 1$, MeOH).

TFA.H-L-Pro-L-Pro-OMe (**C1**)
It was obtained as a pale brown oil (82%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 10.86$ (s, 1H), 7.43 (s, 1H), 4.76 (s, 1H), 4.59 (m, 1H), 3.74 (s, 3H), 3.72–3.40 (m, 4H), 2.62–1.98 (m, 8H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$, POL-P204-13C): $\delta = 171.7$, 167.3, 161.2 (q, $J = 37.6$ Hz), 114.4 (q, $J = 286.9$ Hz), 59.3, 58.7, 52.5, 47.0, 46.8, 28.8, 28.7, 24.7, 24.6 ppm; IR (ATR): $\bar{\nu} = 2962$, 2324, 2118, 2096, 1742, 1655, 1459, 1368, 1260, 1078, 798, 705 cm^{-1}; HRMS: *m/z* calculated for $C_{11}H_{19}N_2O_3$ $[M + H]^+$ 227.1390, found 227.1391; $[\alpha]_D^{20} = -10.6$ ($c = 1$, MeOH). Spectral data agree with those in the literature [56].

TFA.H-D-Pro-L-Glu(OMe)-OMe (**C2**)
It was obtained as a brown oil (95%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 10.57$ (bs, 1H), 8.57 (bs, 1H), 7.59 (s, 1H), 4.75–4.67 (m, 1H), 4.67–4.52 (m, 2H), 3.72 (s, 3H), 3.62 (s, 3H), 3.45 (m, 2H), 2.59–1.93 (m, 8H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 173.0$, 171.8, 169.1, 163.8, 59.7, 52.7, 52.2, 51.9, 46.8, 41.9, 37.2, 32.1, 30.2, 29.8, 27.0, 26.5, 24.4 ppm; IR (ATR): $\bar{\nu} = 3075$, 2959, 2578, 2489, 2330, 2120, 1882, 1730, 1664, 1560, 1438, 1347, 1257, 1160, 1133, 981, 835, 797, 721 cm^{-1}; HRMS: *m/z* calculated for $C_{12}H_{21}N_2O_5$ $[M + H]^+$ 273.1445, found 273.1443; $[\alpha]_D^{20} = -1.5$ ($c = 1$, MeOH).

TFA.H-D-Pro-L-Glu(OH)-OH (**C3**)
It was obtained as a pale brown oil (78%). ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 9.48$ (bs, 1H), 8.56 (bs, 1H), 4.39–4.05 (m, 2H), 3.33–3.06 (m, 2H), 2.40–1.70 (m, 8H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 173.6$, 172.7, 168.4, 158.3 (q, $J = 35.4$ Hz), 119.4 (q, $J = 282.9$ Hz), 59.1, 51.7, 45.7, 29.9, 29.8, 26.3, 23.5 ppm; IR (ATR): $\bar{\nu} = 3442$, 3072, 2959, 2568, 2324, 2117, 2092, 1905, 1719, 1663, 1560, 1411, 1141, 962, 797, 722, 703 cm^{-1}; HRMS: *m/z* calculated for $C_{10}H_{17}N_2O_5$ $[M + H]^+$ 245.1132, found 245.1130; $[\alpha]_D^{20} = -2.9$ ($c = 1$, MeOH).

TFA.H-D-Pro-L-Pro-L-Glu-OH (**C6**)
It was obtained as a pale brown oil (91%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.56$–4.38 (m, 2H), 3.79–3.24 (m, 5H), 2.65–1.78 (m, 11H) ppm; ^{13}C NMR (75 MHz): $\delta = 172.6$, 170.7, 170.4, 164.4, 157.6 (q, $J = 35.5$ Hz), 118.7 (q, $J = 280.9$ Hz), 57.9, 56.7, 49.2, 43.6, 27.3, 26.8, 25.6, 24.1, 21.7, 21.4 ppm; IR (ATR): $\bar{\nu} = 3510$, 3070, 2980, 2715, 2363, 2118, 1998, 1888, 1780, 1719, 1639, 1550, 1451, 1374, 1343, 1144, 797, 722, 699 cm^{-1}; HRMS: *m/z* calculated for $C_{15}H_{24}N_3O_6$ $[M + H]^+$ 342.1660, found 342.1661; $[\alpha]_D^{20} = -0.6$ ($c = 1$, MeOH).

Deprotection of the *N*-Cbz protecting group

The *N*-Cbz-D-Pro-L-Pro-L-Glu(OMe)-OMe was dissolved in 10 cm^3 of methanol and 5.8 mg palladium (0.054 mmol, 10 wt% on activated carbon) was added. The reaction mixture was stirred under hydrogen atmosphere at room temperature 48 h. The solution was filtered over Celite, the solvent was evaporated under reduced pressure, and H-D-Pro-L-Pro-L-Glu(OMe)-OMe was obtained in 93% yield.

H-D-Pro-L-Pro-L-Glu(OMe)-OMe (**C5**)
It was obtained as a mixture of conformers (93%), as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.71–4.41 (m, 3H), 3.86–3.26 (m, 10H), 2.59–1.87 (m, 12H) ppm; ^{13}C NMR (151 MHz): δ = 173.4, 173.1, 172.9, 172.5, 172.2, 172.0, 171.8, 171.7, 171.6, 171.2, 125.3, 67.3, 61.0, 60.4, 59.7, 59.4, 58.9, 55.8, 52.3, 52.0, 51.8, 51.7, 51.6, 51.6, 47.7, 47.3, 47.3, 46.6, 46.5, 40.3, 32.0, 30.4, 30.3, 30.0, 29.7, 29.1, 28.5, 28.3, 28.1, 27.1, 26.9, 26.2, 25.9, 24.8, 24.6, 24.3, 22.9, 22.1 ppm; IR (ATR): $\bar{\nu}$ = 3447, 3199, 2952, 2880, 2782, 2427, 2352, 2253, 2115, 2093, 1933, 1733, 1647, 1541, 1437, 1365, 1341, 1257, 1199, 1168, 1123, 1093, 1039, 1007, 982, 918, 851, 821, 752 cm^{-1}; HRMS: *m/z* calculated for $C_{17}H_{28}N_3O_6$ $[M + H]^+$ 370.1973, found 370.1975; $[\alpha]_D^{20}$ = − 20.7 (*c* = 1, MeOH).

General procedure for Michael addition

Peptide catalyst (0.022 mmol) and 2.2 mg NMM (0.022 mmol) were dissolved in 1.2 cm^3 solution mixture of $CHCl_3$/*i*-PrOH (9:1), and after 10 min, nitroalkene (0.43 mmol) was added and, if applicable, 3 mol% of an acidic additive was added. Again, after 10 min, stirring aldehyde (1.29 mmol) was added dropwise and the resulting reaction mixture was stirred at room temperature. The reaction time was monitored by TLC, followed by concentration in vacuo. The crude product was purified by flash chromatography using Isolera Biotage FSKO-1107-0010 (silica gel, hexane: ethyl acetate gradient 35:1–15:1). The product was obtained in the reported yields with a defined diastereoselectivity and enantioselectivity.

2-Benzyl-3-(furan-2-yl)-4-nitrobutanal (**5a**)
Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.72 (d, *J* = 1.4 Hz, 1H), 9.69 (d, *J* = 1.8 Hz, 1H), 7.40 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.30 (m, 2H), 7.23–7.09 (m, 3H), 6.35 (m, 1H), 6.23 (m, 1H), 4.78–4.58 (m, 2H), 4.08(m, 1H), 3.96 (m, 1H), 3.21–3.04 (m, 1H), 2.94–2.70 (m, 2H) ppm. Spectral data agree with those in the literature [42]. HPLC: Chiralcel AS-H, heptane/*i*-PrOH 90:10, 0.7 cm^3/min, λ = 220 nm, t_{R1} = 29.15, t_{R2} = 39.5 min; $[\alpha]_D^{20}$ = − 3.5 (*c* = 1, $CHCl_3$).

3-(Furan-2-yl)-2-methyl-4-nitrobutanal (**5b**)
Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.71 (s, 1H), 9.64 (d, *J* = 1.30 Hz, 1H), 7.36 (s, 1H), 6.32–6.28 (m, 1H), 6.22–6.16 (m, 1H), 4.80–4.66 (m, 2H), 4.12–3.96 (m, 1H), 2.90–2.73 (m, 1H), 1.24–1.05 (dd, *J* = 36.0, 7.5 Hz, 3H) ppm. Spectral data agree with those in the literature [57]. HPLC: Chiralcel OD-H, hexan/*i*-PrOH 92:8, 0.8 cm^3/min, λ = 250 nm, t_{R1} = 26.3, t_{R2} = 37.8 min; $[\alpha]_D^{20}$ = 2.8 (*c* = 1, $CHCl_3$) ($[\alpha]_D^{20}$ = 17.2 (93% *ee*, *c* = 1, $CHCl_3$ [58]).

2-Ethyl-3-(furan-2-yl)-4-nitrobutanal (**5c**)
Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.72 (d, *J* = 2.0 Hz, 1H), 9.61 (d, *J* = 2.60 Hz, 1H), 7.38–7.35 (dd, *J* = 1.9, 0.7 Hz, 1H), 6.33–6.18 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.22–6.18 (d, *J* = 3.3 Hz, 1H), 4.76–4.60 (m, 2H), 4.05–3.95 (dt, *J* = 8.8, 5.5 Hz, 1H), 2.80–2.71 (m, 1H), 1.22 (d, 3H), 1.08 (d, 3H), 0.91 (t, *J* = 7.5 Hz, 3H) ppm. Spectral data agree with those in the literature [50]. HPLC: Chiralcel OD-H, hexane/*i*-PrOH 95:5, 0.8 cm^3/min, λ = 250 nm, t_{R1} = 33.0, t_{R2} = 50.2 min; $[\alpha]_D^{20}$ = 0.4 (*c* = 1, $CHCl_3$).

2-[1-(Furan-2-yl)-2-nitroethyl]pentanal (**5d**)
Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.71 (d, *J* = 2.1 Hz, 1H), 9.60 (d, *J* = 2.7 Hz, 1H), 7.36 (d, *J* = 1.7 Hz, 1H), 6.31 (dd, *J* = 3.1, 1.8 Hz, 1H), 6.19 (dd, *J* = 3.4 Hz, 1H), 4.77–4.61 (m, 1H), 4.07–3.92 (m, 1H), 2.83–2.57 (m, 1H), 1.56–1.34 (m, 4H), 0.88 (t, *J* = 7.0 Hz, 1H) ppm. Spectral data agree with those in the literature [59]. $[\alpha]_D^{20}$ = − 6.3 (*c* = 1, $CHCl_3$).

2-[1-(Furan-2-yl)-2-nitroethenyl]octanal
(**5e**, $C_{14}H_{21}NO_4$)
Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.65 (d, *J* = 1.9 Hz, 1H), 9.60 (d, *J* = 2.6 Hz, 1H), 7.40–7.32 (m, 1H), 6.31 (m, 1H), 6.19 (m, 1H), 4.76–4.60 (m, 2H), 4.00 (m, 1H), 2.83–2.54 (m, 1H), 1.74–1.13 (m, 10H), 0.86 (t, *J* = 6.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.4, 150.1, 142.6, 110.5, 108.8, 76.1, 52.3, 37.0, 31.4, 29.2, 26.9, 26.6, 22.5, 14.0 ppm; IR (ATR): $\bar{\nu}$ = 2926, 2857, 2727, 2090, 1720, 1553, 1506, 1459, 1431, 1376, 1191, 1148, 1075, 968, 915, 810, 736, 645, 598 cm^{-1}. HRMS: *m/z* calculated for $C_{14}H_{21}NO_4$ Na-adduct $[M + Na]^+$ 290.1363, found 290.1364; $[\alpha]_D^{20}$ = − 18.7 (*c* = 1, $CHCl_3$).

2-[1-(Furan-2-yl)-2-nitroethyl]cyclopentanone (**7a**)
Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33 (d, *J* = 1.0 Hz, 1H), 6.33–7.26 (m, 1H), 6.14 (dd, *J* = 6.9, 3.2 Hz, 1H), 5.09–4.95 (dd, *J* = 13.1, 6.2 Hz, 1H), 4.96–4.72 (m, 2H), 4.04–3.91 (m, 1H), 2.54–1.55 (m, 6H) ppm; HPLC: Chiralcel AS-H, heptane/*i*-PrOH 90:10, 0.7 cm^3/min, λ = 230 nm, t_{R1} = 32.9, t_{R2} = 55.8 min. Spectral data agree with those in the literature [60].

2-[1-(Furan-2-yl)-2-nitroethyl]cyclohexanone (**7b**)
Pale yellow solid. M.p.: 82–84 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.36$–7.32 (m, 1H), 6.31–6.26 (dd, $J = 3.2$, 1.9 Hz, 1H), 6.17 (m, 1H), 4.82–4.76 (dd, $J = 12.5$, 4.9 Hz, 1H), 4.71–4.62 (dd, $J = 12.5$, 9.2 Hz, 1H), 4.02–3.92 (dt, $J = 9.1$, 4.9 Hz, 1H), 2.81–2.69 (m, 1H), 2.51–2.29 (m, 2H), 2.15–2.05 (m, 1H), 1.88–1.60 (m, 4H), 1.28 (m, 1H) ppm. Spectral data agree with those in the literature [48]. HPLC: Chiralcel IA, hexane/*i*-PrOH 90:10, 0.7 cm^3/min, $\lambda = 254$ nm, $t_{R1} = 17.1$, $t_{R2} = 21.0$ min; $[\alpha]_D^{20} = 0.5$ ($c = 1$, $CHCl_3$) using **C4**; $[\alpha]_D^{20} = -11.2$ ($c = 1$, $CHCl_3$) using **C3**.

Acknowledgements This work was supported by the Slovak Research and Development Agency under the contract no. APVV-15-0039.

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