Facile Access to Unnatural Dipeptide-Alcohols Based on cis-2,5-Disubstituted Pyrrolidines

Yan-Yan Jia 1,†, Xiao-Ye Li 2,†, Ping-An Wang 2,* and Ai-Dong Wen 1,*

1 Department of Pharmacy, Xijing Hospital, Fourth Military Medical University, Changle West Road 15, Xi’an 710032, China; E-Mail: xjyypharmacy@126.com
2 Department of Medicinal Chemistry, School of Pharmacy, Fourth Military Medical University, Changle West Road 169, Xi’an 710032, China; E-Mail: lixiaoye@fmmu.edu.cn

† These authors contributed equally to this work.

* Authors to whom correspondence should be addressed;
E-Mails: ping_an1718@outlook.com (P.-A.W.); adwen@fmmu.edu.cn (A.-D.W.);
Tel.: +86-29-84776807 (ext. 605) (P.-A.W.); Fax: +86-29-84776945 (P.-A.W.).

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Abstract: Well-defined unnatural dipeptide-alcohols based on a cis-2,5-disubstituted pyrrolidine backbone were synthesized from commercially available starting materials meso-diethyl-2,5-dibromoadipate, (S)-(−)-1-phenylethylamine, and phenylalaninol. The structures of these unnatural dipeptide-alcohols are supported by HRMS, 1H- and 13C-NMR spectroscopy. These unnatural dipeptide-alcohols can act as building blocks for peptidomimetics.

Keywords: cis-2,5-disubstituted pyrrolidine; unnatural dipeptide-alcohol; hydrogenolysis; phenylalaninol

1. Introduction

The unnatural peptide-alcohols are important building blocks for the construction of peptide derivatives and play a vital role in peptidomimetics [1–4]. Some natural pepta-antibiotics [5,6] possessing unnatural peptide-alcohol motifs are isolated from fungus, such as leucinostatins [7], culicinins [8] and hirsuitatins [9]. The unnatural peptide-alcohols that possess a pyrrolidine ring are also
attractive to chemists and pharmaceutists [10,11]. Pei and colleagues discovered a series of unnatural peptide-alcohols with one cis-2,5-disubstituted pyrrolidine backbone as potent dipeptidyl peptidase IV (DPP-IV) inhibitors for potential oral anti-diabetic drugs [12,13]. Colandrea and researchers [14] reported several 2,5-disubstituted pyrrolidine carboxylic acids that are potent, orally active sphingosine-1-phosphate (S1P) receptor agonists. Aurantiamide, the major isolated component from Zanthoxylum dissitum and Aspergillus penicilloides, contains one phenyalaninol motif and exhibits anti-bacterial, anti-inflammatory, antioxidant, and anti-HIV effects [15]. Furthermore, Yen et al. [16], have developed a series of aurantiamide acetate analogs bearing a phenyalaninol group which were used as potent anti-inflammatory agents.

In our previous work, we reported the efficient construction of enantiopure unsymmetric cis-2,5-disubstituted pyrrolidines (Figure 1, compounds A–D) using meso-diethyl-2,5-dibromoadipate and (S)-(−)-1-phenylethylamine as starting materials [17–19]. Herein, we describe a facile route to unnatural dipeptide-alcohols from phenylalaninol and cis-2,5-disubstituted pyrrolidines.

![Figure 1. Some novel unsymmetrical cis-2,5-disubstituted pyrrolidines.](image)

2. Results and Discussion

The monoacid cis-1 can be obtained by both chemical and enzymatic protocols via the monohydrolysis of diethyl cis-1-[(S)-1-phenylethyl]pyrrolidine-2,5-dicarboxylate [20]. In the presence of KOH/EtOH, monoacid cis-1 was obtained in 76% yield as a light yellow slurry. Using the conventional peptide-synthetic protocol, the coupling reactions of L- and D-phenylalaninol with monoacid cis-1 were investigated, respectively. The couplings were performed smoothly by using 1.5 equiv. of dicyclohexylcarbodiimide (DCC) as a coupling reagent in dry CH2Cl2 at room temperature (rt) (Scheme 1). Both the diastereomers cis-2 and cis-3 were obtained in good yields (up to 80%). Interestingly, the diastereomeric mixture cis-2 prepared from L-phenylalaninol and monoacid cis-1 was easily separated to be (−)-4a and (+)-4b by a flash column chromatography (FC) on silica gel, however, the diastereomeric mixture cis-3, the coupling product obtained from monoacid cis-1 and D-phenylalaninol instead could not be separated as two compounds by flash column chromatography (Scheme 2). The diastereomeric ratio of the major and the minor component in cis-3 is 2/1 which was deduced from its 1H-NMR spectrum.
Scheme 1. Synthesis of cis-2 and cis-3.

Scheme 2. Synthetic routes to (−)-5a and (−)-5b.

In the presence of catalytic quantity of Pd(OH)₂/C and under H₂ atmosphere, compounds (−)-4a and (+)-4b were converted to be the corresponding deprotected dipeptide-alcohols (−)-5a and (−)-5b with one protected carboxylic group and one C-terminal hydroxyl group, respectively (Scheme 2). The dipeptide-alcohols (−)-5a and (−)-5b containing a cis-pyrrolidine backbone with one free N-terminal at pyrrolidine ring and one C-terminal hydroxyl group in the side-chain can be used as valuable building blocks for connection of other amino acids to furnish complex peptide-alcohols.

Hydrolysis of compounds (−)-4a and (+)-4b using solid KOH in THF/H₂O afforded the corresponding dipeptide-alcohols (−)-6a and (−)-6b with free C-terminal carboxylic acid and hydroxyl groups (Scheme 3). These free carboxylic acid and hydroxyl groups can enable the coupling with other amino acids to yield complex unnatural peptide-alcohols. The other two unnatural dipeptide-alcohols
(--)-7a and (--)-7b with both free C- and N-terminus were obtained by catalytic hydrogenolysis of compounds (--)-6a and (--)-6b in methanol at room temperature separately.

Scheme 3. Synthetic routes to (--)-7a and (--)-7b.

3. Experimental Section

3.1. General Information

Melting points are uncorrected and expressed in °C. 1H- and 13C-NMR spectra were measured in CDCl3, MeOD or DMSO-d6 solution on a Bruker AV-300 or AV-500 spectrometers (Bruker, Fällanden, Switzerland) using TMS as an internal reference. Multiplicities are designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet. Optical rotations analyses were performed on a Model 343 Polarimeter (Perkin-Elmer, Waltham, MA, USA). High-resolution mass spectra were performed on a VG Micromass 7070F Mass Spectrometer (VG Instruments, St Leonards-on-Sea, UK) with ES ionization (ESI). All commercially available reagents were used as received. Products were purified by flash column chromatography on silica gel purchased from Qingdao Haiyang Chemical Co. Ltd. (Qingdao, China). All reactions involving air or moisture sensitive species were performed in oven-dried glassware under inert atmosphere. The monoacid cis-1 was prepared following the reported procedures in the previous literature [17].

3.1.1. Typical Procedure for cis-2 or cis-3

To a mixture of monoacid cis-1 (2.90 g, 10.0 mmol) and L-phenylalaninol (1.60 g, 10.5 mmol) in dry CH2Cl2 (50 mL), DCC (3.20 g, 15.5 mmol) and DMAP (125 mg, 1.0 mmol) added at 0 °C, and the mixture was stirred for 0.5 h at this temperature and stirred overnight at rt. After the reaction was finished, it was filtered on a Celite pad. The solvents was evaporated to give cis-2 (diastereomeric mixture) as a yellow oil which was purified by a flash column chromatography on silica gel to afford (--)-4a and (+)-4b. The coupling product cis-3 (diastereomeric mixture) was obtained by the similar procedure from D-phenylalaninol (0.79 g, 5.2 mmol) and monoacid cis-1 (1.46 g, 5.0 mmol), and it could not be separated by a flash column chromatography.

cis-Ethyl 5-{{[(R)-1-hydroxy-3-phenylpropan-2-yl]carbamoyl}-1-[[S]-1-phenylethyl]pyrrolidine-2-carboxylate (cis-3 diastereomeric mixture). 1.82 g, 85%; light yellow wax. 1H-NMR (500 MHz, CDCl3):
Major isomer: δH 1.25 (t, J = 7.0 Hz, 2H), 1.34 (d, J = 5.5 Hz, 2H), 1.79–2.11 (m, 2.5 H), 2.82–3.02 (m, 2H), 3.45–3.48 (m, 1H), 3.55–3.68 (m, 1H), 3.81–3.87 (m, 1H), 3.99–4.08 (m, 1H), 4.11–4.16 (m, 1H), 7.07–7.34 (m, 10H), 8.46 (d, J = 8.5 Hz, 0.66H). Minor isomer: δ 1.18 (t, J = 7.5 Hz, 1H), 8.88 (d, J = 9.0 Hz, 0.33H), the other signals are overlapped with the major isomer. HRMS (ESI) m/z calcd for C25H33N2O4 (MH+): 425.2440. Found: 425.2451.

(2S,5R)-Ethyl 5-[(S)-1-hydroxy-3-phenylpropan-2-yl]carbamoyl]-1-[(S)-1-phenylethyl]pyrrolidine-2-carboxylate (−)-4a. 1.53 g, 37%; light yellow solid, mp 89.5–91 °C, Rf = 0.30 (n-hexane/EtOAc, 2:1), [α]D20 +71.6 (c 0.5, CHCl3). 1H-NMR (300 MHz, CDCl3): δH 1.28 (t, J = 7.2 Hz, 3H), 1.38 (d, J = 6.9 Hz, 3H), 1.79–1.87 (m, 2H), 1.91–2.01 (m, 2H), 2.75 (br, 1H), 2.89 (dd, J1 = 8.4 Hz, J2 = 5.7 Hz, 1H), 3.02 (dd, J1 = 7.5 Hz, J2 = 6.6 Hz, 1H), 3.61–3.76 (m, 4H), 3.86 (q, J = 6.9 Hz, 1H), 4.16 (q, J = 7.2 Hz, 2H), 4.20–4.30 (m, 1H), 7.17–7.33 (m, 10H), 8.65 (d, J = 8.1 Hz, 1H). 13C NMR (300 MHz, CDCl3): δC 14.3, 19.4, 30.2, 30.7, 36.8, 52.8, 61.1, 61.5, 64.0, 65.1, 65.4, 126.4, 127.6, 127.7, 128.3, 128.5, 129.2, 138.2, 142.3, 175.9, 176.3. HRMS (ESI) m/z calcd for C25H33N2O4 (MH+) : 425.2440. Found: 425.2458.

(2R,5S)-Ethyl 5-[(S)-1-hydroxy-3-phenylpropan-2-yl]carbamoyl]-1-[(S)-1-phenylethyl]pyrrolidine-2-carboxylate (+)-4b. 1.91 g, 45%; light yellow solid, mp 101.5–103.7 °C, Rf = 0.30 (n-hexane/EtOAc, 2:1), [α]D20 +18.2° (c 1.05, CHCl3). 1H-NMR (300 MHz, CDCl3): δH 1.12 (t, J = 7.2 Hz, 3H), 1.26 (d, J = 6.9 Hz, 3H), 1.63–1.74 (m, 1H), 1.93–2.01 (m, 3H), 2.87–3.03 (m, 2H), 3.39 (t, J = 6.9 Hz, 1H), 3.57–3.78 (m, 5H), 3.88–4.05 (m, 2H), 4.18–4.28 (m, 1H), 7.19–7.35 (m, 10H). 13C-NMR (300 MHz, MeOD): δC 13.1, 20.1, 30.1, 30.7, 36.6, 52.3, 60.7, 62.8, 63.0, 65.2, 66.1, 126.1, 127.2, 128.0, 128.2, 128.9, 138.3, 142.8, 176.7, 176.9. HRMS (ESI) m/z calcd for C25H33N2O4 (MH+) : 425.2440. Found: 425.2447.

3.1.2. Typical Procedure for (−)-5a or (−)-5b

In the presence of Pd(OH)2/C (0.20 g), the compound (−)-4a (0.50 g, 1.17 mmol) in MeOH (10.0 mL) was stirred overnight under 1.0 atm H2 at rt. After the reaction was finished, it was filtered on a Celite pad to remove catalyst. The filtrate was evaporated to give the desired product (−)-5a without further purification. Compound (−)-5b was obtained from (+)-4b by the similar procedure.

(2S,5R)-Ethyl 5-[(S)-1-hydroxy-3-phenylpropan-2-yl]carbamoyl]pyrrolidine-2-carboxylate (−)-5a. Light yellow crystals, 0.35 g, 92%, mp 52–53.5 °C, [α]D20 +210.5° (c 1.0, MeOH). 1H-NMR (300 MHz, CDCl3): δH 1.31 (t, J = 7.0 Hz, 3H), 1.62–1.66 (m, 1H), 1.90–1.94 (m, 1H), 2.11–2.18 (m, 2H), 2.87–2.97 (m, 2H), 3.50–3.65 (m, 1H), 3.71–3.74 (m, 1H), 3.98–4.07 (m, 1H), 4.17–4.30 (m, 3H), 7.19–7.29 (m, 5H), 8.45 (d, J = 8.0 Hz, 1H). 13C-NMR (300 MHz, CDCl3): δC 13.3, 29.2, 30.7, 36.7, 52.3, 60.7, 62.8, 63.0, 65.2, 66.1, 126.1, 127.2, 128.0, 128.2, 128.9, 138.3, 142.8, 176.7, 176.9. HRMS (ESI) m/z calcd for C17H26N2O4 (MH+) : 321.1814. Found: 321.1832.

(2R,5S)-Ethyl 5-[(S)-1-hydroxy-3-phenylpropan-2-yl]carbamoyl]pyrrolidine-2-carboxylate (−)-5b. Colorless crystals, 0.34 g, 90%, mp 71–73 °C, [α]D20 −3.6° (c 0.5, DMSO). 1H-NMR (300 MHz, MeOD): δH 1.28 (t, J = 7.2 Hz, 3H), 1.69–1.87 (m, 2H), 2.0–2.18 (m, 2H), 2.77 (dd, J = 8.7, 5.1 Hz, 1H), 2.98
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(dd, J = 7.8, 5.7 Hz, 1H), 3.56 (t, J = 5.7 Hz, 2H), 3.68–3.72 (m, 1H), 3.93 (t, J = 7.5 Hz, 1H), 4.05–4.14 (m, 1H), 4.19 (q, J = 7.2 Hz, 2H), 7.12–7.23 (m, 5H). $^{13}$C-NMR (500 MHz, DMSO-$d_6$): $\delta$C 14.5, 30.1, 31.4, 37.1, 52.4, 60.2, 60.8, 61.4, 62.9, 126.4, 128.6, 129.6, 139.3, 173.8, 175.2. HRMS (ESI) m/z calcd for C$_{17}$H$_{26}$N$_2$O$_4$ (MH$^+$): 321.1814. Found: 321.1839.

3.1.3. Typical Procedure for (−)-6a or (−)-6b

The compound (−)-4a (1.0 g, 2.35 mmol) in THF/H$_2$O (1:1) (15 mL) was added by KOH pellets (0.33 g, 4.7 mmol) and the mixture was stirred 2 h at rt. After the reaction was finished, the solvent was evaporated and the acidity of the aqueous residue was adjusted to be pH = 2.0 by 6.0 M HCl, then it was extracted by ethyl acetate (3 × 10 mL), the combined organic layer was washed by H$_2$O (2 × 5 mL) and brine (10 mL), dried (Na$_2$SO$_4$). The solvent was evaporated under reduced pressure to give the desired product (−)-6a without further purification. Compound (−)-6b was obtained from (−)-4b by the similar procedure.

(2S,5R)-5-[(S)-1-Hydroxy-3-phenylpropan-2-yl]carbamoyl]-1-[(S)-1-phenylethyl]pyrrolidine-2-carboxylic acid (−)-6a. Colorless powder, 0.85 g, 91%, mp 182.5–183.5 °C, $[\alpha]_D^0$ −65.5° (c 0.3, MeOH). $^1$H-NMR (300 MHz, MeOD): $\delta$H 1.20 (d, J = 9.0 Hz, 3H), 1.24–1.32 (m, 1H), 1.42–1.48 (m, 1H), 1.68–1.92 (m, 2H), 2.59 (dd, J = 9.6, 4.5 Hz, 1H), 2.95 (dd, J = 9.0, 4.8 Hz, 1H), 3.54 (dd, J = 7.2, 1.5 Hz, 1H), 3.81 (q, J = 6.6 Hz, 1H), 3.91–4.02 (m, 1H), 4.92 (br, 1H), 7.11–7.29 (m, 10H), 8.42 (d, J = 9.0 Hz, 1H). $^{13}$C-NMR (300 MHz, MeOD): $\delta$C 21.0, 30.0, 30.1, 37.3, 52.2, 61.7, 63.6, 64.6, 65.2, 126.4, 127.6, 128.4, 128.7, 129.4, 139.5, 143.8, 174.3, 177.6. HRMS (ESI) m/z calcd for C$_{23}$H$_{29}$N$_2$O$_4$ (MH$^+$): 397.2127. Found: 397.2139.

(2R,5S)-5-[(S)-1-Hydroxy-3-phenylpropan-2-yl]carbamoyl]-1-[(S)-1-phenylethyl]pyrrolidine-2-carboxylic acid (−)-6b. Colorless crystals, 0.83 g, 90%, mp 188–190 °C, $[\alpha]_D^0$ −39.2° (c 0.25, MeOH).

$^1$H-NMR (300 MHz, MeOD): $\delta$H 1.35 (d, J = 6.9 Hz, 3H), 1.59–1.72 (m, 1H), 1.83–2.14 (m, 2H), 2.72 (dd, J = 9.6, 4.5 Hz, 1H), 3.04 (dd, J = 8.4, 5.7 Hz, 1H), 3.55 (dd, J = 5.4 Hz, 2H), 3.81 (q, J = 7.8 Hz, 2H), 4.06–4.21 (m, 2H), 7.17–7.40 (m, 11H). $^{13}$C-NMR (300 MHz, MeOD): $\delta$C 20.2, 30.3, 31.2, 37.0, 52.4, 61.7, 63.0, 64.5, 65.9, 126.3, 127.5, 127.8, 128.4, 128.5, 129.3, 129.3, 139.0, 143.0, 175.3, 177.3. HRMS (ESI) m/z calcd for C$_{23}$H$_{29}$N$_2$O$_4$ (MH$^+$): 397.2127. Found: 397.2141.

3.1.4. Typical Procedure for the Synthesis of (−)-7a or (−)-7b

In the presence of Pd(OH)$_2$/C (0.23 g), the compound (−)-6a (0.60 g, 1.5 mmol) in MeOH (8 mL) was stirred overnight under 1.0 atm H$_2$ at rt. After the reaction was finished, it was filtered on a Celite pad to remove catalyst. The filtrate was evaporated to give the desired product (−)-7a without further purification. Compound (−)-7b was obtained from (−)-6b by the similar procedure.

(2S,5R)-5-[(S)-1-Hydroxy-3-phenylpropan-2-yl]carbamoyl]pyrrolidine-2-carboxylic acid (−)-7a. Colorless powder, 0.38 g, 87%, mp 197–199 °C, $[\alpha]_D^0$ −36.7° (c 0.125, MeOH). $^1$H-NMR (300 MHz, DMSO-$d_6$): $\delta$H 1.25–1.35 (m, 1H), 1.69–1.77 (m, 1H), 1.91–2.05 (m, 2H), 2.59 (dd, J = 9.0, 4.5 Hz, 1H), 2.88 (dd, J = 8.7, 5.1 Hz, 1H), 3.55–3.69 (m, 2H), 3.83 (t, J = 7.5 Hz, 1H), 3.92–3.99 (m, 1H), 7.14–7.28 (m, 5H), 8.33 (d, J = 9.0 Hz, 1H). $^{13}$C-NMR (500 MHz, DMSO-$d_6$): $\delta$C 29.8, 30.8, 36.9, 53.2, 60.7, 60.8,
62.9, 126.5, 128.4, 129.5, 139.4, 170.9, 173.2. HRMS (ESI) m/z calcd for C_{15}H_{21}N_{2}O_{4} (MH^+): 293.1501. Found: 293.1496.

(2R,5S)-5-\{[(S)-1-Hydroxy-3-phenylpropan-2-yl]carbamoyl\}pyrrolidine-2-carboxylic acid (−)-7b. Colorless powder, 0.40 g, 91%, mp 212–214 °C, [\alpha]_D^{20} \text{−}10.2^\circ (c 0.2, MeOH). \textsuperscript{1}H-NMR (500 MHz, DMSO-d_6): \delta_H 1.25–1.35 (m, 1H), 1.70–1.79 (m, 1H), 1.96–2.10 (m, 2H), 2.62 (dd, J = 9.0, 4.5 Hz, 1H), 2.89 (dd, J = 8.5, 5.0 Hz, 1H), 3.10–3.60 (m, 1H, overlap), 3.88 (t, J = 7.0 Hz, 1H), 3.90–4.02 (m, 1H), 4.93 (br, 1H), 7.16–7.27 (m, 5H), 8.42 (d, J = 8.0 Hz, 1H). \textsuperscript{13}C-NMR (500 MHz, DMSO-d_6): \delta_C 29.9, 30.6, 37.1, 53.2, 60.6, 61.0, 63.2, 126.5, 128.5, 129.6, 139.2, 169.8, 172.2. HRMS (ESI) m/z calcd for C_{15}H_{21}N_{2}O_{4} (MH^+): 293.1501. Found: 293.1496.

4. Conclusions

A facile route to unnatural dipeptide-alcohols based on a cis-2,5-disubstituted pyrrolidine backbone that is readily prepared from commercially available materials is described. Two distereomers are separated by simple flash column chromatography, and these unnatural peptide-alcohols contain a free C-terminus, a C-terminal hydroxyl group or a N-terminus that can facilitate couplings with other amino acids to give more complex polypeptide alcohols.

Supplementary Materials

Supplementary materials can be accessed at: http://www.mdpi.com/1420-3049/20/02/2922/s1.

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Author Contributions

Y.Y. Jia synthesized compounds 4–7, and X.Y. Li prepared compounds 2 and 3 in multi-gram scale for materials of preparation of 4–7, A.D. Wen interpreted the NMR spectra of all compounds and prepared the manuscript. P.A. Wang instructed the whole work.

Conflicts of Interest

The authors declare no conflict of interest.

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*Sample Availability*: Samples of the compounds are available from the authors.

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