Molecules **2015**, *20*, 2922-2930; doi:10.3390/molecules20022922

OPEN ACCESS

molecules

ISSN 1420-3049

www.mdpi.com/journal/molecules

Article

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.).

Academic Editor: Panayiotis Koutentis

Received: 11 December 2014 / Accepted: 30 January 2015 / Published: 11 February 2015

Abstract: Well-defined unnatural dipeptide-alcohols based on a *cis*-2,5-disubstitued 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, ^{1}H- and ^{13}C-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.

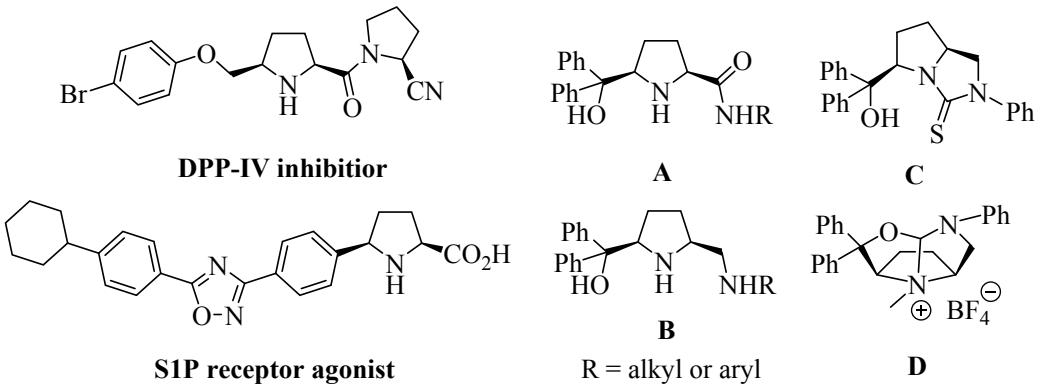
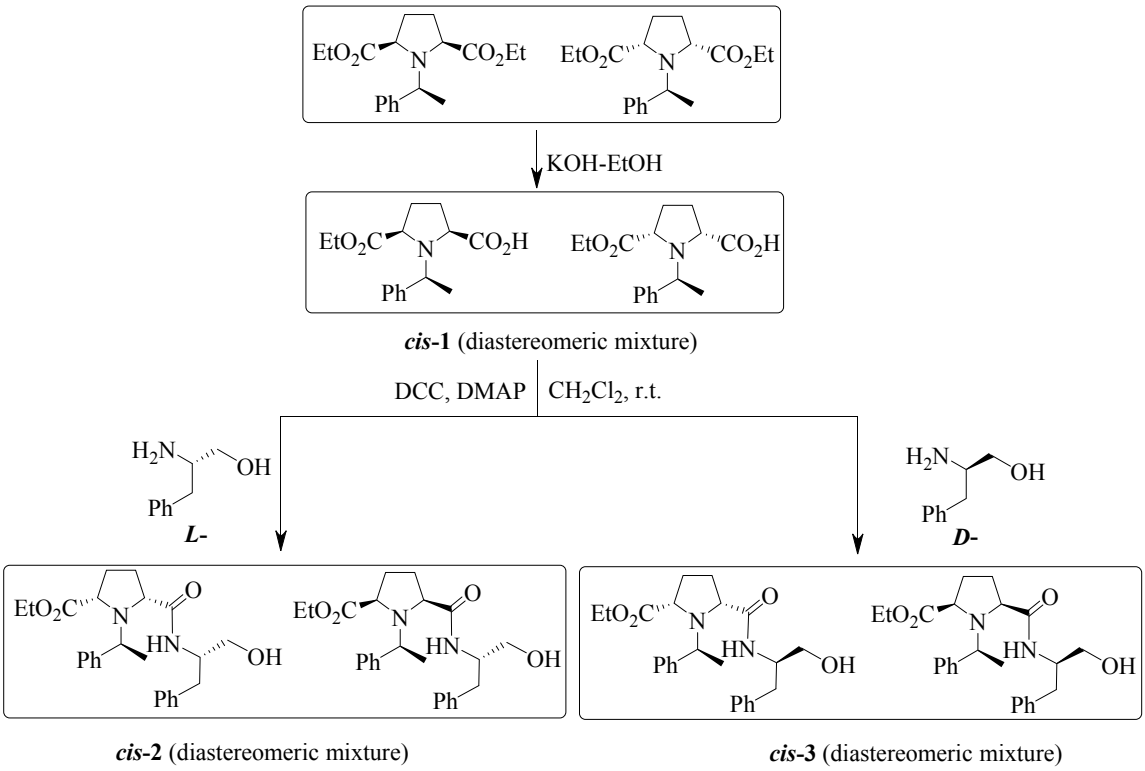


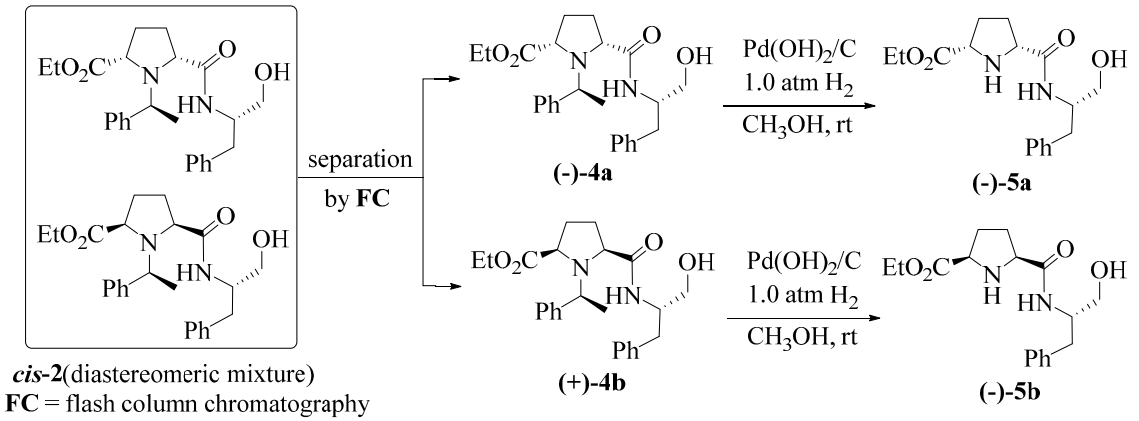
Figure 1. Some novel unsymmetrical *cis*-2,5-disubstituted pyrrolidines.

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 CH_2Cl_2 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 ^{1}H-NMR spectrum.



Scheme 1. Synthesis of *cis*-**2** and *cis*-**3**.

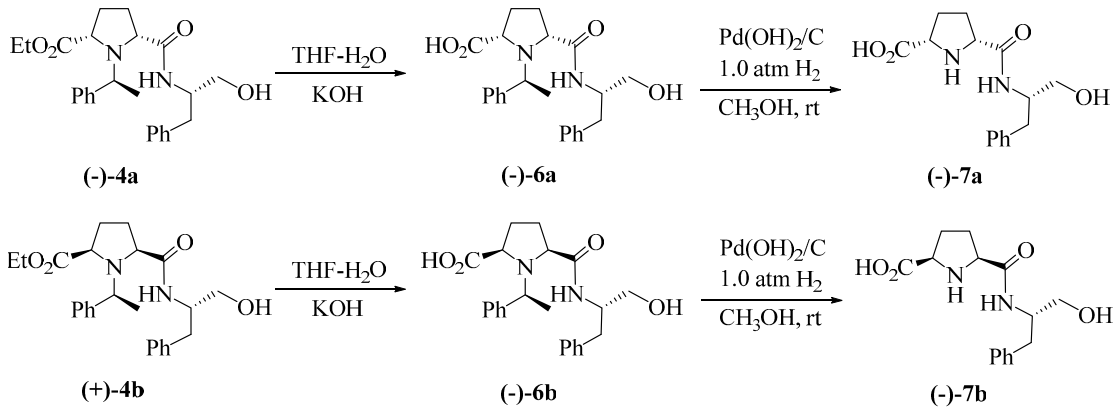


Scheme 2. Synthetic routes to **(−)-5a** and **(−)-5b**.

In the presence of catalytic quantity of $Pd(OH)_2/C$ and under H_2 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/H_2O 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. ^{1}H- and ^{13}C-NMR spectra were measured in $CDCl_3$, MeOD or DMSO-d_6 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 CH_2Cl_2 (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. ^{1}H-NMR (500 MHz, $CDCl_3$):

Major isomer: δ_H 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, 3H), 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 $C_{25}H_{33}N_2O_4$ (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, R_f = 0.50 (*n*-hexane/EtOAc, 2:1), $[\alpha]_D^{20}$ −71.6 (*c* 0.5, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H 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, J_1 = 8.4 Hz, J_2 = 5.7 Hz, 1H), 3.02 (dd, J_1 = 7.5 Hz, J_2 = 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). ^{13}C NMR (300 MHz, CDCl3): δ_C 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 $C_{25}H_{33}N_2O_4$ (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, R_f = 0.30 (*n*-hexane/EtOAc, 2:1), $[\alpha]_D^{20}$ +18.2° (*c* 1.05, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H 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), 8.81 (d, J = 8.1 Hz, 1H). ^{13}C-NMR (300 MHz, MeOD) δ_C 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 $C_{25}H_{33}N_2O_4$ (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 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 **(−)-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, $[\alpha]_D^{20}$ −210.5° (*c* 1.0, MeOH). ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 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). ^{13}C-NMR (300 MHz, $CDCl_3$): δ_C 13.3, 29.2, 30.7, 36.7, 52.1, 59.9, 60.7, 61.3, 63.3, 125.9, 127.8, 128.9, 138.4, 175.7, 175.9. HRMS (ESI) *m/z* calcd for $C_{17}H_{26}N_2O_4$ (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, $[\alpha]_D^{20}$ −3.6° (*c* 0.5, DMSO). ^{1}H-NMR (300 MHz, MeOD): δ_H 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

(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*$_6$): δ_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 $C_{17}H_{26}N_2O_4$ (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_2O (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_2O (2 × 5 mL) and brine (10 mL), dried (Na_2SO_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, $[\alpha]_D^{20}$ −65.5° (*c* 0.3, MeOH). ^{1}H-NMR (300 MHz, MeOD): δ_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): δ_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 $C_{23}H_{29}N_2O_4$ (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, $[\alpha]_D^{20}$ −39.2° (*c* 0.25, MeOH). ^{1}H-NMR (300 MHz, MeOD): δ_H 1.35 (d, *J* = 6.9 Hz, 3H), 1.59–1.72 (m, 1H), 1.83–1.92 (m, 1H), 2.01–2.14 (m, 2H), 2.72 (dd, *J* = 9.6, 4.5 Hz, 1H), 3.04 (dd, *J* = 8.4, 5.7 Hz, 1H), 3.55 (d, *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): δ_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 $C_{23}H_{29}N_2O_4$ (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, $[\alpha]_D^{20}$ −36.7° (*c* 0.125, MeOH). ^{1}H-NMR (300 MHz, DMSO-*d*$_6$): δ_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*$_6$): δ_C 29.8, 30.8, 36.9, 53.2, 60.7, 60.8,

62.9, 126.5, 128.4, 128.6, 129.5, 139.4, 170.9, 173.2. HRMS (ESI) *m/z* calcd for $C_{15}H_{21}N_2O_4$ (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, $[\alpha]_D^{20}$ −10.2° (*c* 0.2, MeOH). ^{1}H-NMR (500 MHz, DMSO-d_6): δ_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). ^{13}C-NMR (500 MHz, DMSO-d_6): δ_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 $C_{15}H_{21}N_2O_4$ (MH^+): 293.1501. Found: 293.1510.

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.

Acknowledgments

We thank the grants from the National Science Foundation of China (No. 21372259), the National Science and Technology Major Project of the Ministry of Science and Technology of China (No.2012BAK25B00) and the China Postdoctoral Science Foundation Grant (2014M552706) for financial support of this work.

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.