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ORIGINAL ARTICLE

Efficient synthesis of unnatural dipeptides based on *cis*-2,5-disubstituted pyrrolidine

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Abstract The well-defined unnatural dipeptides based on *cis*-2,5-disubstituted pyrrolidine backbone were synthesized from commercially available starting materials *meso*-diethyl-2,5-dibromoadipate, (*S*)-(−)-1-phenylethylamine, and phenylalanine. The configurations of all the chiral centers in these unnatural dipeptides are confirmed by X-ray crystal diffraction analysis.

Keywords *cis*-2,5-Disubstituted pyrrolidine · Unnatural dipeptide · Phenylalanine · X-ray diffraction analysis

Introduction

The unnatural peptides play a key role in peptidomimetics (Sun et al. 2008; Hanessian and Auzzas 2008; Isidro-Llobet et al. 2011; Ung and Winkler 2011), among them peptides containing 2,5-disubstituted pyrrolidine moiety have drawn much attention of chemists and pharmaceutists by their unique physiological activities (Wang et al. 2001; Enache et al. 2009; Davis et al. 2008; Draper and Britton 2010). Due to non-planar nature of pyrrolidine, peptides containing pyrrolidine motif can have flexible conformation which is responsible for their biological activities (Madis 1977; Giordano et al. 2010; Warren et al. 2010). Pei et al. (2006) have found a series of unnatural dipeptides based on *cis*-2,5-disubstituted pyrrolidine backbone which were used as potent dipeptidyl peptidase IV (DPP-IV) inhibitors for potential anti-diabetic drugs. Manfré and Pulicani (1994) synthesized a unnatural dipeptide (+)-RP-66803 with *cis*-2,5-disubstituted pyrrolidine core as a cholecystokinin (CCK) antagonist (Fig. 1). The compounds containing 2,5-disubstituted pyrrolidine ring are also attractive to synthetic chemists by their versatile utilities in organic synthesis (Vaswani et al. 2009; Lemen and Wolfe 2010; Chen et al. 2009; Shu et al. 2010). Some important alkaloids, such as cocaine (Lewin et al. 1987; Mans and Pearson 2004), gephyrotoxin (Miao et al. 2010) and monomorine (Jefford et al. 1991), possess *cis*-2,5-disubstituted pyrrolidine ring system. The synthesis of several indolizidine alkaloids containing a chiral *trans*-2,5-disubstituted pyrrolidine moiety was described (Dhimane et al. 1997; Takahata et al. 1990; Wang et al. 1999; Lee et al. 2000; Cahill et al. 1999); however, only few methods provide stereoselective synthesis of *cis*-2,5-disubstituted pyrrolidine derivatives (Haddad et al. 1998; Brenneman and Martin 2004; Bagley and Tovey 2001; Colandrea et al. 2006). Lygo et al. (2010) have described a synthetic route to *cis*-2,5-disubstituted pyrrolidine derivatives by asymmetric phase-transfer catalysis. Previously, we have reported a facile access to enantiopure *cis*-2,5-disubstituted pyrrolidines (Fig. 1, compounds **A** and **B**) using *meso*-diethyl-2,5-dibromoadipate and (*S*)-(−)-1-phenylethylamine as starting materials (Wang et al. 2007). With this background and in continuation of our previous work, we report in this paper an efficient construction of unnatural dipeptides from phenylalanine and *cis*-2,5-disubstituted pyrrolidines. In which configuration of the chiral centers was confirmed by X-ray crystallographic analysis.

Electronic supplementary material The online version of this article (doi:10.1007/s00726-011-0949-4) contains supplementary material, which is available to authorized users.

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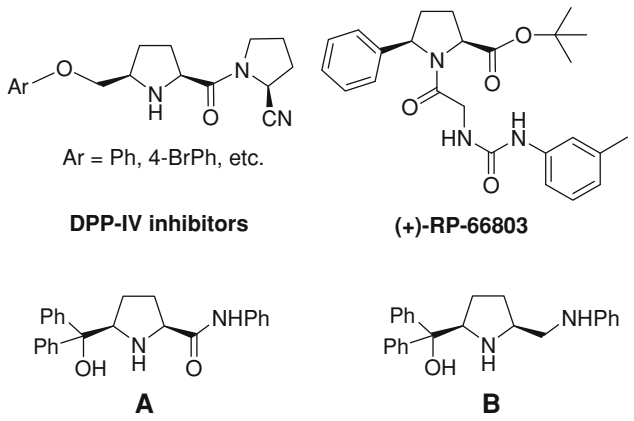


Fig. 1 Some novel unsymmetric *cis*-2,5-disubstituted pyrrolidines

Experimental

General

^{1}H NMR and ^{13}C NMR spectra were measured in $CDCl_3$, MeOD or DMSO-D_6 solution on a Bruker AV-300 or AV-500 spectrometer using TMS as an internal reference. Coupling constant (J) values are given in Hz. Multiplicities are designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet. Mass spectra and high-resolution mass spectra were performed on a VG Micromass 7070F Mass Spectrometer with ES ionization (ESI). X-ray diffraction analysis was measured using a Bruker SMART CCD Single Crystal X-ray Diffractometer; the structure was solved by direct methods and refined on F^2 by full-matrix least-squares methods using *SHELXL-97* (Sheldrick 2008). Melting points are uncorrected and expressed in °C. Optical rotations analyses were performed on a Perkin-Elmer Model 343 Polarimeter. High-resolution mass spectra were performed on a VG Micromass 7070F Mass Spectrometer 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. All reactions involving air or moisture sensitive species were performed in oven-dried glassware under inert atmosphere.

Typical procedure for ***cis*-2** or ***cis*-3**

To a mixture of monoacid ***cis*-1** (1.52 g, 5.2 mmol) and L-phenylalanine ethyl ester hydrochloride (1.26 g, 5.5 mmol) in dry CH_2Cl_2 (30.0 mL), Et_3N (2.0 mL, 14.2 mmol) was added at −5°C under nitrogen, and the mixture was stirred for 1.0 h at r.t., dicyclohexylcarbodiimide (DCC) (1.6 g, 7.5 mmol) and DMAP (60 mg, 0.5 mmol) were added to the mixture at −5°C and the mixture was stirred overnight. After the reaction was finished, it was filtered on a Celite pad. The filtrate was evaporated to give ***cis*-2** (diastereomeric mixture) as yellow oil. The residue was purified by silica gel column chromatography to give the desired compounds **(−)-4a** and **(−)-4b**.

(−)-4a, *n*-hexane/ethyl acetate = 3:1 (v/v), $R_f = 0.45$, yield: 1.02 g (41% yield), light yellow oil; **(−)-4b**, *n*-hexane/ethyl acetate = 3:1 (v/v), $R_f = 0.35$, yield: 1.24 g (49% yield), light yellow oil.

The coupling product ***cis*-3** (diastereomeric mixture, 2.25 g, 95% yield) was obtained by the similar procedure from D-phenylalanine ethyl ester hydrochloride and monoacid ***cis*-1**, and it could not be separated by a column chromatography.

Spectroscopic data for compound: ***cis*-3** *(diastereomeric mixture)*

^{1}H NMR (500 MHz, $CDCl_3$): major isomer: δ 1.10–1.13 (m, 2.5H), 1.20–1.30 (m, 4H), 1.30–1.40 (m, 2.5H), 1.51–1.59 (m, 1H), 1.72–1.88 (m, 1H), 2.01 (m, 1H), 3.06–3.15 (m, 1H), 3.30–3.38 (m, 1H), 3.51–3.54 (m, 1H), 3.58–3.70 (m, 1H), 3.80–3.90 (m, 1H), 3.91–4.02 (m, 1H), 4.13–4.25 (m, 1H), 4.97 (m, 0.74H), 7.20–7.42 (m, 10H), 8.86 (m, 0.73H). Minor isomer: δ 4.65–4.75 (m, 0.20 H), 8.88 (m, 0.20 H), the other signals are overlapped with the major isomer. HRMS (ESI) *m*/*z* calcd for $C_{27}H_{35}N_2O_5$ (M+H): calcd 467.2546, obs 467.2540. Light yellow oil, $[\alpha]_D^{25} = -21.4°$ ($c = 0.58$, $CHCl_3$).

Spectroscopic data for compound: ***(−)-4a***

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24 (t, $J = 7.0$ Hz, 3H), 1.29 (t, $J = 7.0$ Hz, 3H), 1.41 (d, $J = 6.5$ Hz, 3H), 1.74–1.91 (m, 4H), 3.06 (dd, $J_1 = 8.5$ Hz, $J_2 = 5.5$ Hz, 1H), 3.31 (dd, $J_1 = 8.5$ Hz, $J_2 = 5.5$ Hz, 1H), 3.62 (dd, $J_1 = 7.5$ Hz, $J_2 = 2.5$ Hz, 1H), 3.68 (dd, $J_1 = 5.5$ Hz, $J_2 = 2.5$ Hz, 1H), 3.94 (q, $J = 7.0$ Hz, 1H), 4.08–4.17 (m, 2H), 4.25 (q, $J = 7.5$ Hz, 2H), 4.92–4.97 (m, 1H), 7.20–7.30 (m, 10H), 8.83 (d, $J = 9.0$ Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 14.2, 14.3, 18.8, 29.9, 30.8, 38.3, 52.8, 60.6, 60.9, 61.2, 63.8, 64.2, 126.7, 127.4, 127.8, 128.2, 128.4, 129.2, 136.7, 141.7, 171.7, 175.1, 175.7. HRMS (ESI) *m*/*z* calcd for $C_{27}H_{35}N_2O_5$ (M+H): calcd 467.2546, obs 467.2542. Yellow oil, $[\alpha]_D^{25} = -32.4°$ ($c = 1.06$, $CHCl_3$).

Spectroscopic data for compound: ***(−)-4b***

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.14 (t, $J = 7.0$ Hz, 6H), 1.25 (t, $J = 7.0$ Hz, 3H), 1.69–2.01 (m, 4H), 3.10 (dd,

$J_1 = 9.5$ Hz, $J_2 = 5.0$ Hz, 1H), 3.32 (dd, $J_1 = 8.5$ Hz, $J_2 = 5.5$ Hz, 1H), 3.58 (q, $J = 7.0$ Hz, 2H), 3.68 (q, $J = 7.0$ Hz, 1H), 3.97 (m, 2H), 4.01–4.22 (m, 2H), 4.80–4.84 (m, 1H), 7.14–7.40 (m, 10H), 8.76 (d, $J = 8.0$ Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 14.1, 14.2, 20.9, 30.6, 31.0, 37.6, 53.4, 60.8, 61.2, 62.8, 64.9, 66.4, 126.9, 127.5, 128.0, 128.3, 128.5, 129.2, 136.9, 142.4, 171.8, 175.8, 176.1. HRMS (ESI) *m/z* calcd for $C_{27}H_{35}N_2O_5$ (M+H): calcd 467.2546, obs 467.2550. Yellow oil, $[\alpha]_D^{25} = -89.4^\circ$ ($c = 1.23$, $CHCl_3$).

Typical procedure for unnatural dipeptide **(+)-5a** or **(+)-5b**

In the presence of $Pd(OH)_2/C$ (0.12 g), the compound **(−)-4a** (0.52 g, 1.11 mmol) in MeOH (6.0 mL) was stirred overnight under 1.0 atm H_2 at r.t. 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** (yellow crystal, 0.38 g, 96% yield) without further purification.

Compound **(+)-5b** was obtained from **(−)-4b** by the similar procedure in 94% yield (white crystal, 0.43 g).

Spectroscopic data for compound: ***(+)-5a***

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.27 (t, $J = 7.0$ Hz, 3H), 1.29 (t, $J = 7.0$ Hz, 3H), 1.53–1.61 (m, 2H), 1.82–1.90 (m, 1H), 2.01–2.08 (m, 1H), 2.86 (br, 1H), 3.03 (dd, $J_1 = 8.1$ Hz, $J_2 = 5.7$ Hz, 1H), 3.21 (dd, $J_1 = 8.1$ Hz, $J_2 = 6.0$ Hz, 1H), 3.82–3.87 (m, 1H), 3.91–3.96 (m, 1H), 4.12–4.23 (m, 1H), 4.83–4.91 (m, 1H), 7.18–7.28 (m, 5H), 8.50 (d, $J = 8.4$ Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 14.1, 14.3, 29.6, 31.2, 38.2, 52.9, 60.3, 61.0, 61.2, 61.3, 126.7, 128.2, 128.3, 129.3, 136.5, 171.8, 174.5, 174.9. HRMS (ESI) *m/z* calcd for $C_{19}H_{27}N_2O_5$ (M+H): calcd 363.1920, obs 363.1929. Yellow crystal, m.p. 54.5–56.0°C, $[\alpha]_D^{25} = +4.5^\circ$ ($c = 1.0$, $CHCl_3$).

Spectroscopic data for compound: ***(+)-5b***

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (t, $J = 7.2$ Hz, 3H), 1.27 (t, $J = 7.2$ Hz, 3H), 1.90–2.17 (m, 4H), 2.66 (br, 1H), 3.06 (dd, $J_1 = 8.7$ Hz, $J_2 = 5.7$ Hz, 1H), 3.20 (dd, $J_1 = 8.4$ Hz, $J_2 = 5.4$ Hz, 1H), 3.75–3.85 (m, 1H), 3.90–3.96 (m, 1H), 4.12–4.23 (m, 1H), 4.68–4.75 (m, 1H), 7.21–7.32 (m, 5H), 8.55 (d, $J = 7.5$ Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 14.1, 14.2, 29.8, 31.4, 37.8, 53.6, 60.3, 61.1, 61.4, 126.8, 128.4, 129.0, 129.3, 136.8, 171.5, 174.6, 175.5. HRMS (ESI) *m/z* calcd for $C_{19}H_{27}N_2O_5$ (M+H): calcd 363.1920, obs 363.1893. White crystal, m.p. 81.0–82.0°C, $[\alpha]_D^{25} = +13.9^\circ$ ($c = 1.05$, $CHCl_3$).

Typical procedure for unnatural dipeptide **(−)-6a** or **(−)-6b**

The compound **(−)-4a** (0.95 g, 2.1 mmol) in the mixed solvent of THF and H_2O (10.0 mL, v/v = 1:1) was added by KOH pellets (0.36 g, 5.1 mmol) and the mixture was stirred 2 h at r.t. After the reaction was finished, the solvent was evaporated and the acidity of the aqueous residue was adjusted to be pH 3.0 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 over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give the desired product **(−)-6a** as white powder (0.83 g, 96% yield) without further purification.

Compound **(−)-6b** was obtained from **(−)-4b** by the similar procedure in 94% yield (white crystal, 0.80 g).

Spectroscopic data for compound: ***(−)-6a***

^{1}H NMR (500 MHz, DMSO-D_6): δ 1.27 (d, $J = 7.0$ Hz, 3H), 1.30 (m, overlap, 1H), 1.45 (m, 1H), 1.77–1.89 (m, 2H), 2.83 (dd, $J_1 = 10.0$ Hz, $J_2 = 4.0$ Hz, 1H), 3.17 (dd, $J_1 = 9.5$ Hz, $J_2 = 4.5$ Hz, 1H), 3.47 (m, 1H), 3.59 (m, 1H), 3.90 (m, 1H), 4.57–4.61 (m, 1H), 7.18–7.32 (m, 10H), 8.79 (d, $J = 9.0$ Hz, 1H), 12.8 (br, 2H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 20.9, 29.9, 30.6, 37.9, 53.1, 61.4, 64.5, 64.7, 126.9, 127.5, 127.9, 128.5, 128.7, 129.4, 143.5, 173.3, 174.6, 177.5. HRMS (ESI) *m/z* calcd for $C_{23}H_{27}N_2O_5$ (M+H): calcd 411.1920, obs 411.1912. White powder, m.p. 193.5–194.5°C, $[\alpha]_D^{25} = -43.4^\circ$ ($c = 0.55$, DMSO).

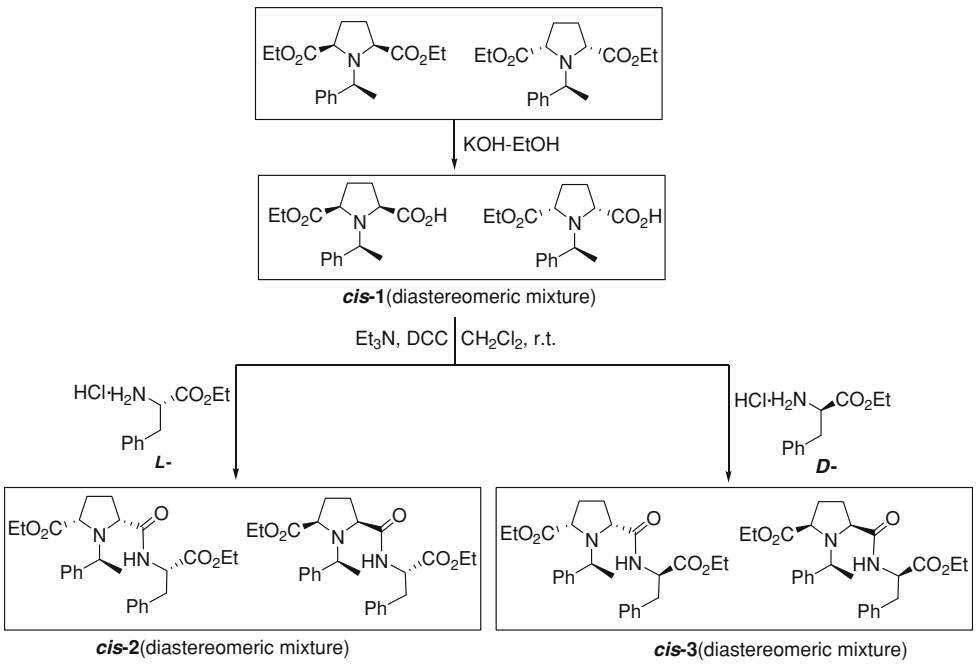
Spectroscopic data for compound: ***(−)-6b***

^{1}H NMR (500 MHz, DMSO-D_6): δ 1.03 (d, $J = 7.0$ Hz, 3H), 1.69–1.80 (m, 2H), 1.89–1.99 (m, 2H), 2.85 (dd, $J_1 = 11.0$ Hz, $J_2 = 3.0$ Hz, 1H), 3.22 (dd, $J_1 = 9.5$ Hz, $J_2 = 4.5$ Hz, 1H), 3.44 (m, 1H), 3.51 (m, 1H), 3.72 (m, 1H), 4.39–4.44 (m, 1H), 7.14–7.36 (m, 10H), 8.80 (d, $J = 7.5$ Hz, 1H), 12.6 (br, 2H). ^{13}C NMR (300 MHz): δ 20.8, 29.6, 31.0, 38.2, 52.8, 60.6, 63.9, 64.2, 126.7, 127.2, 128.0, 128.7, 128.9, 129.2, 142.9, 172.3, 174.8, 178.0. HRMS (ESI) *m/z* calcd for $C_{23}H_{27}N_2O_5$ (M+H): calcd 411.1920, obs 411.1914. White powder, m.p. 201.0–203.0°C, $[\alpha]_D^{25} = -60.8^\circ$ ($c = 0.4$, DMSO).

Typical procedure for unnatural dipeptide **(+)-7a** or **(+)-7b**

In the presence of $Pd(OH)_2/C$ (0.13 g), the compound **(−)-6a** (0.61 g, 1.5 mmol) in MeOH (6.0 mL) was stirred

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



overnight under 1.0 atm H_2 at r.t. 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** as white powder (0.42 g, 91% yield) without further purification.

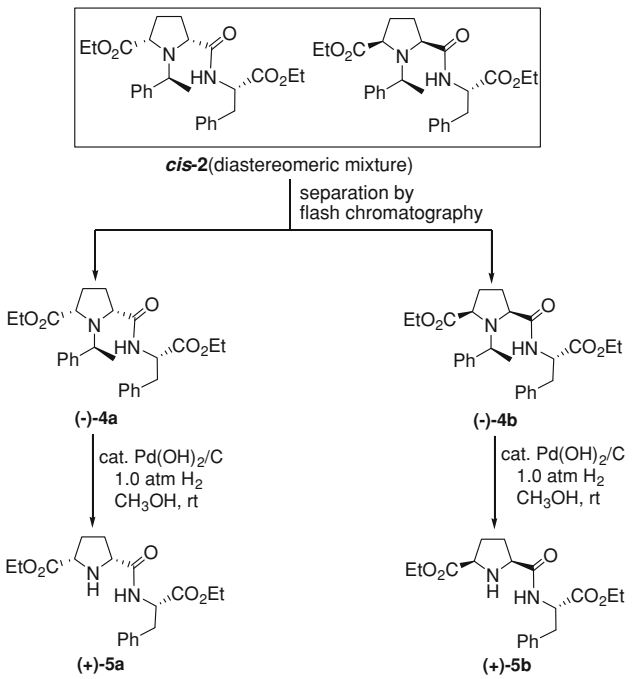
Compound **(+)-7b** was obtained from **(−)-6b** by the similar procedure in 89% yield (white powder, 0.40 g).

Spectroscopic data for compound: ***(+)-7a***

^{1}H NMR (300 MHz, DMSO-D_6): δ 1.49–1.61 (m, 1H), 1.67–1.80 (m, 1H), 1.95–2.11 (m, 2H), 2.63 (dd, $J_1 =$ 8.7 Hz, $J_2 = 5.1$ Hz, 1H), 2.83 (dd, $J_1 = 7.8$ Hz, $J_2 = 5.7$ Hz, 1H), 3.71–3.75 (m, 1H), 3.80–3.85 (m, 1H), 3.88–3.96 (m, 1H), 4.94 (br, 1H), 7.15–7.28 (m, 5H), 8.38 (d, $J = 8.4$ Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 30.2, 31.4, 38.8, 54.3, 61.8, 62.4, 127.1, 128.6, 129.2, 129.6, 141.5, 172.3, 176.6, 177.2. HRMS (ESI) *m*/*z* calcd for $C_{15}H_{19}N_2O_5$ (M+H): calcd 307.1294, obs 307.1298. White powder (very hygroscopic), $[\alpha]_D^{25} = +11.6°$ ($c =$ 0.5, DMSO).

Spectroscopic data for compound: ***(+)-7b***

^{1}H NMR (300 MHz, DMSO-D_6): δ 1.25–1.30 (m, 1H), 1.70–1.77 (m, 1H), 1.97–2.05 (m, 2H), 2.55–2.63 (m, 1H), 2.85–2.91 (m, 1H), 3.67–3.71 (m, 1H), 3.88–4.02 (m, 2H), 4.96 (br, 1H), 7.14–7.27 (m, 5H), 8.42 (d, $J = 8.7$ Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 28.2, 32.1, 37.4, 55.6, 60.9, 61.7, 126.9, 127.8, 128.8, 129.5, 139.8, 171.4, 175.7, 176.1. HRMS (ESI) *m*/*z* calcd for $C_{15}H_{19}N_2O_5$ (M+H): calcd 307.1294, obs 307.1290. White powder (very hygroscopic), $[\alpha]_D^{25} = +25.2°$ ($c =$ 0.5, DMSO).



Scheme 2 Synthetic routes to unnatural dipeptides **(+)-5a** and **(+)-5b**

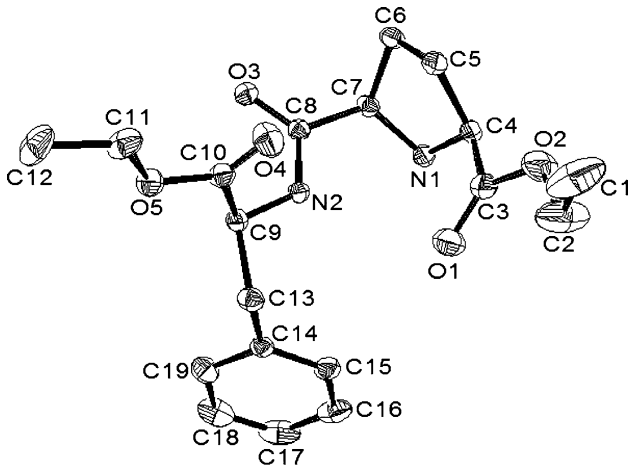


Fig. 2 ORTEP diagram of compound **(+)-5a**

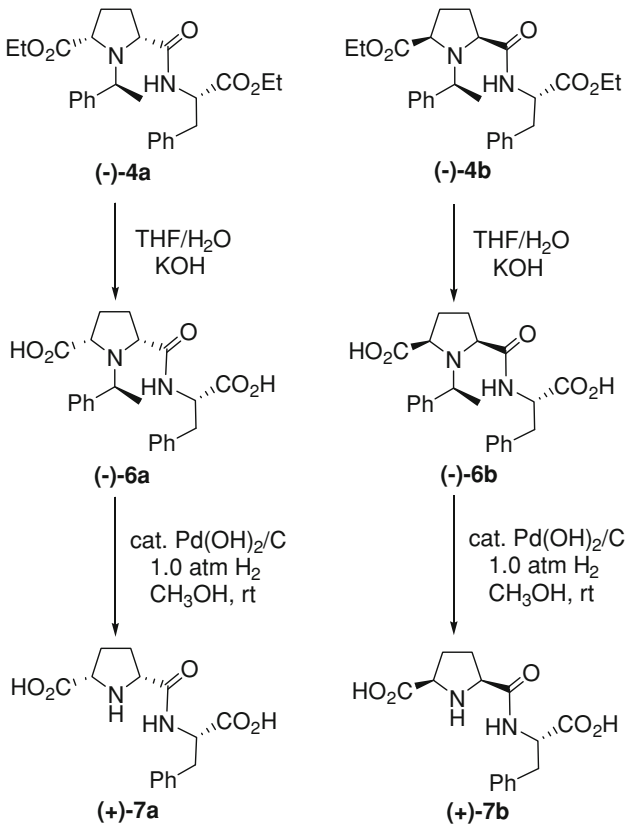
Result and discussion

The monoacid ***cis*-1** was obtained in 76% yield by previously reported protocol of selective monohydrolysis (Wang et al. 2007) of diethyl *cis*-1-[(*S*)-1-phenylethyl]pyrrolidine-2,5-dicarboxylate (Yamamoto et al. 1993). The coupling reactions of monoacid ***cis*-1** with L- and D-phenylalanine ethyl ester hydrochloride were investigated, respectively. In the presence of triethylamine, the coupling of phenylalanine ethyl ester hydrochlorides with monoacid ***cis*-1** was performed smoothly using 1.5 equiv. DCC as coupling reagent and CH_2Cl_2 as solvent at room temperature (Scheme 1). Both ***cis*-2** and ***cis*-3** were obtained in excellent yields (up to 95%). To our delight, the diastereomeric mixture ***cis*-2** prepared from L-phenylalanine ethyl ester 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** prepared from monoacid ***cis*-1** and D-phenylalanine ethyl ester instead could not be separated by the column chromatography (Scheme 2). We could deduce from ^{1}H NMR spectrum that the diastereomeric ratio of the major and the minor in ***cis*-3** is about 3.5/1.

Consequently, compounds **(−)-4a** and **(−)-4b** were hydrogenolysed using catalytic amount of $Pd(OH)_2/C$ in methanol to afford the corresponding dipeptides **(+)-5a** and **(+)-5b** with protected carboxylic groups, respectively (Scheme 2). The dipeptides **(+)-5a** and **(+)-5b** containing *cis*-pyrrolidine structure with free *N*-terminal at pyrrolidine

Table 1 Crystallographical and experimental data for compounds **(+)-5a**

Compound	**(+)-5a**
Formula	$C_{19}H_{26}N_2O_5$
MW	362.42
Crystal system	Orthorhombic
Space group	*P*2(1)2(1)2(1)
a (Å)	9.0797(17)
b (Å)	12.392(2)
c (Å)	17.930(3)
α (°)	90
β (°)	90
γ (°)	90
Volume (Å^3)	2,017.4(6)
Z	4
D_c (g cm^{-3})	1.193
μ (mm^{-1})	0.087
F(000)	776
θ range (°)	2.00/25.10
Index ranges	$-10 \le h \le 10$, $-8 \le k \le 14$, $-21 \le l \le 21$
Reflections collected/unique	10,083/3,592 (R_{int} 0.0286)
Observed reflections	2,401
Goodness-of-fit on F^2	1.005
Final *R* indices, $I \ge 2\sigma(I)$	R_1 0.0410, wR_2 0.1118
R indices (all data)	R_1 0.0619, wR_2 0.1195
Largest diff. peak and hole (eÅ^{-3})	0.204 and −0.227



Scheme 3 Synthetic routes to unnatural dipeptides **(+)-7a** and **(+)-7b**

ring can be served as valuable building blocks for connection of other amino acids to furnish some other complicated peptides.

Fortunately, compound **(+)-5a** got crystallized from CH_2Cl_2. The X-ray diffraction analysis (Fig. 2) shows the *cis*-configuration at C4 and C7. The crystal packing is found to be orthorhombic. The absolute configurations of C4, C7 and C9 of **(+)-5a** were deduced from the starting material L-phenylalanine, which should be *S*, *R* and *S*, separately. Some crystal data of **(+)-5a** are listed in Table 1.

Hydrolysis of compounds **(−)-4a** and **(−)-4b** using solid KOH in THF-H_2O afforded the corresponding dipeptides **(−)-6a** and **(−)-6b** with two free C-termini (Scheme 3) and these free carboxylic groups provide the possibilities for bonding some other amino acids to yield complex unnatural peptides. The other two unnatural dipeptides **(+)-7a** and **(+)-7b** with both free C- and N-terminus were obtained by $Pd(OH)_2$/C catalytic hydrogenolysis of compounds **(−)-6a** and **(−)-6b** in methanol at room temperature separately. The compounds **(+)-7a** and **(+)-7b** found to be hygroscopic.

Conclusion

In summary, we provide a simple and efficient construction of unnatural dipeptides based on *cis*-2,5-disubstituted pyrrolidine backbone from commercially available starting materials, and these unnatural peptides contain free C-terminus or N-terminus which are convenient to couple with the other amino acids to give more complex polypeptides. The configurations of these unnatural dipeptides are confirmed by X-ray crystal diffraction analysis. The synthesis of some novel bioactive cyclic peptides derived from these unnatural dipeptides is currently investigated in our laboratory.

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