Asymmetric synthesis of non-natural amino acid derivatives: (2*R*/3*S*) and (2*S*/3*R*) 2-(*tert*-butoxycarbonylamino)-3-cyclohexyl-3-phenyl propanoic acids

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Highly conformationally-constrained novel α-amino acid derivatives ((2*R*/3*S*) and (2*S*/3*R*)-2-(*tert*-butoxycarbonylamino)-3-cyclohexyl-3-phenylpropanoic acids) have been synthesised with high stereoselectivity (>90% *de*) and in 36–37% overall yields. In the synthesis, Evans' auxiliary (4(*R*/*S*)-4-phenyl-oxzaolidin-2-one) was used to control the stereoselectivity *via* the key reactions of asymmetric Michael addition, azidation and catalytic hydrogenolysis.

Keywords: non-natural amino acid, oxazolidinone, asymmetric synthesis, chiral auxiliary, β-cyclohexylphenylalanine

Peptides and proteins, along with their receptors/targets, are important chemical couriers because they affect all vital processes of human and animal biology. A central objective in modern peptide chemistry, as well as medicinal and organic chemistry, is to develop efficient approaches to understand the relationships between structure, conformation, dynamics, and biological activities so as to design receptor type-selective and subtype-selective peptide and peptidomimetic ligands with specific conformational and topographical features.[1] Incorporation of conformationally-constrained novel β-branched α-amino acids into bioactive peptides introduces conformational constraints that have been used to obtain important information on receptor-site structure and to optimise therapeutic activity.[2–6] This has resulted in the development of a vast number of methods for the asymmetric synthesis of non-proteinogenic α-amino acids.[5–8] Among them, Hruby and colleagues developed an asymmetric synthetic methodology for the synthesis of highly conformationally-constrained α-amino acids that contain two chiral centres, and a series of specialised α-amino acids were synthesised (Fig. 1).[2–6,9–17] Aromatic and acyclic derivatives are among the numerous types of amino acids that constitute these groups. Aromatic ring-substituted amino acids act as valuable tools in developing highly selective peptide ligands with specific structural features. In addition, they can provide a large lipophilic surface for binding to receptors and for crossing membrane barriers.[9–12] Therefore, the design and synthesis of such unusual β-branched amino acids with lipophilic and cyclic side-chain groups have been critical for the development of peptides and peptide analogues (Fig. 1).

As illustrated in Fig. 1, our target amino acids contain two side chain groups, a phenyl and an alicyclic group. The combination of 4-substituted phenyl and alicyclic groups may significantly increase the hydrophobic interactions of peptide ligands with a receptor/acceptor. Thus, peptide ligands containing these unusual chimeric amino acids may possess unique physico-chemical and conformational properties, improve binding affinity and provide useful information about the stereochemical requirements for peptide ligand–receptor interactions. We now describe the details of the asymmetric synthesis of the novel sterically constrained amino acid derivatives, 2-(*tert*-butoxycarbonylamino)-3-cyclohexyl-3-phenylpropanoic acids **5a** and **5b**.

Results and discussion

As shown in Scheme 1, the synthesis started from a readily available starting material, *trans*-cinnamic acid, which was coupled with optically pure Evans' auxiliaries (4*R*) or (4*S*)-4-phenyl-oxazolidin-2-one to yield the imide conjugates **1a** and **1b**. In this step, phosphorus oxychloride was found to be the best reagent for the coupling reaction, which proceeded conveniently under mild conditions with excellent yields.[19] Then, the chiral Michael acceptors **1a** or **1b** were reacted with cyclohexyl-MgBr under catalysis by the copper(I) bromide-dimethyl sulfide complex *via* an asymmetric conjugate addition to produce the key intermediates **2a** or **2b** using the reported optimised conditions.[13–17,20] In the asymmetric 1,4-Michael addition reactions, Hruby and colleagues found that different 4-substituted compounds were obtained in good yield and optical purity. They studied the mechanism using an NMR method and they also demonstrated the crystal structure by X-ray analysis.[9] However, in our reaction the selectivity was not as good (*de* –85%, as determined by ^{1}H NMR spectroscopy). It was presumed that this was due to the conformational flexibility of cyclohexyl.[21] As a result, we had to purify the products by column chromatography to give the desired corresponding optically pure **2a** or **2b** (*de*>90%), which led to lower yields.

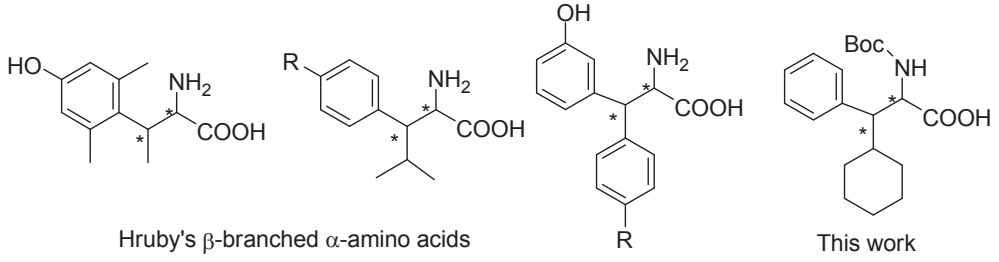

Fig. 1 Highly conformationally-constrained α-amino acids.

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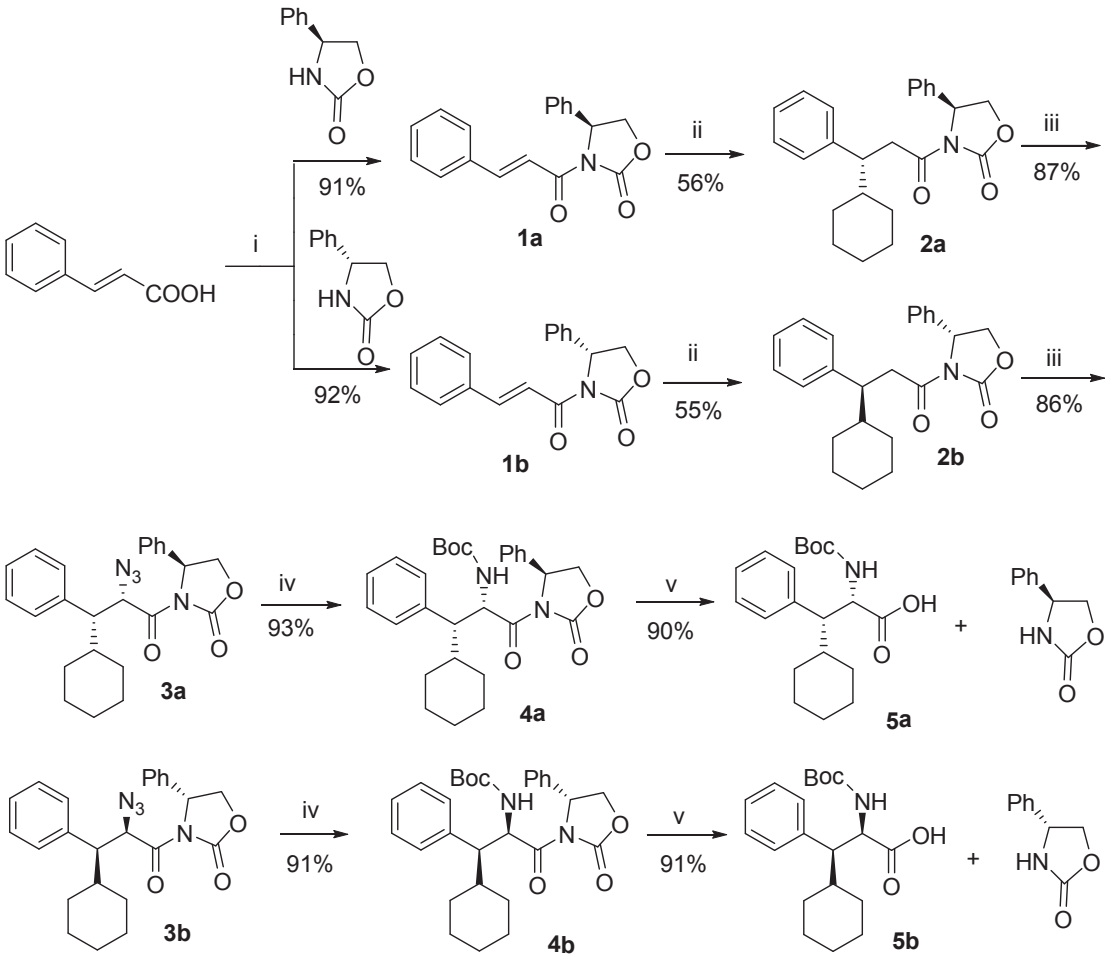


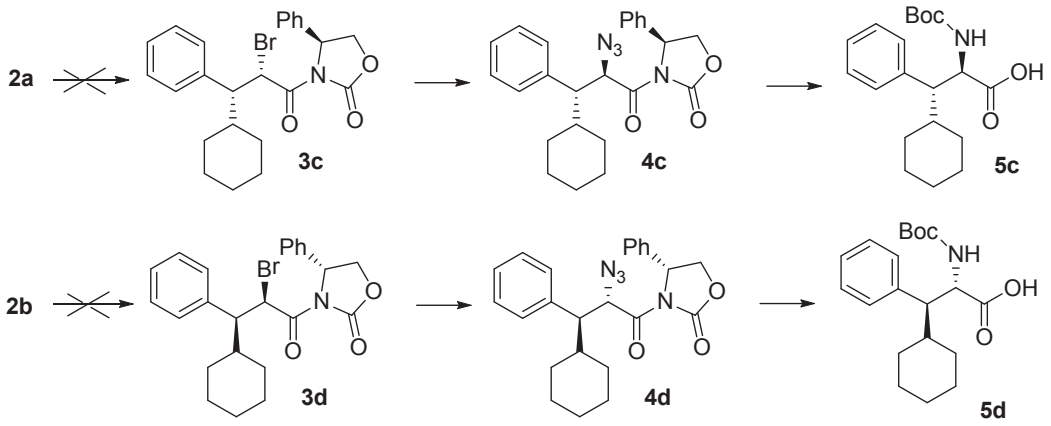
Scheme 1 Reagents and conditions: (i) $POCl_3$, 70 °C; (ii) cyclohexyl-MgBr, CuBr·Me_2S, THF, N_2, –78 °C; (iii) (a) KHMDS/NaH, Trisyl azide; THF, N_2, –78 °C; (b) HOAc, KOAc, 35–40 °C; (iv) hydrogen (H_2), 10%Pd/C, EtOAc, $(Boc)_2O$; (v) $LiOH/H_2O_2$, THF/H_2O, 0 °C.

Our target amino acid has two chiral centres which generated four stereo isomers. In order to synthesise all four isomers, we used Hruby's approach as a guide. Introduction of the azido group to β-aryl derivatives can be accomplished either by direct or indirect azidation which led to diastereoselective syntheses of (*R*)- and (*S*)-α-azido carboxylic acids.[9] Following this procedure, the α-azido derivatives **3a** and **3b** with high diastereoselectivity were produced by direct azidation of intermediates **2a** or **2b** with trisyl azide according to the literatures.[15,16] However, we failed to synthesise the other two isomers, **4c** and **4d**. We originally expected to perform stereoselective bromination of **2a** and **2b** with NBS followed by S_N2 displacement of the bromo group with tetramethylguanidium azide to give α-azido products with a different α-configuration. Unfortunately, the bromination reaction with NBS did not work under any conditions just as indicated by our previous work,[15,16] and the reason is still not clear. Next, the azido acids **3a** or **3b** were subjected to catalytic hydrogenation (H_2, Pd/C, 2.5 h) and the resulting amines were protected as Boc derivatives *in situ*.[22] The removal of the chiral auxiliary from compounds **4a** or **4b** was effected by using LiOH in the presence of hydrogen peroxide to produce final amino acids **5a** or **5b** respectively. At the same time, the chiral auxiliary was recovered in 73% yield and >90% *ee*. We have not been able to obtain the other pair of amino acid derivatives, (2*R*/3*R*) and (2*S*/3*S*) 2-(*tert*-butoxycarbonylamino)-3-cyclohexyl-3-phenylpropanoic acids (**5c** and **5d**) (Scheme 2).

In summary, the stereoselective synthesis of a pair of individual isomers of novel alicyclic-substituted constrained phenylalanine analogues has been achieved. The Evans' chiral auxiliary 4(*R*/*S*)-4-phenyloxazolidin-2-one provides highly stereoselective control of the whole synthesis *via* asymmetric 1,4-Michael addition, direct azidation, one-pot hydrogenolysis, amine protection and hydrolysis reactions with a greater than 90% *de* and 36–37% overall yields. The target compounds represent attractive conformationally-constrained amino acids that may be incorporated into peptidomimetic structures with potential biological activities. Further application of these compounds for the preparation of novel non-proteinogenic α-amino acids is currently underway.

Experimental

All reactions were monitored by TLC; TLC was performed on silica gel GF_{254}. Flash column chromatography was performed on silica gel (200–300 mesh). Melting points were measured on a XT4A temperature apparatus and were uncorrected. Optical rotations were measured on a JASCO DIP-370 polarimeter. NMR spectra were recorded on a Bruker DRX 500 NMR spectrometer and chemical shifts were expressed in ppm (δ) relative to TMS as the internal standard; *J* values are given in Hz. The IR spectra were recorded on a FTIR EQUNOX 55 IR spectrophotometer with KBr pellets. High-resolution mass spectra (HRMS) were determined on VG Auto Spec-3000 spectrometer. Diastereometric excesses (*de*) were determined on Bruker AM-500 spectrometer. All reagents were commercially available and used without further purification. THF was freshly distilled from Na before use.



Scheme 2

Synthesis of compounds **1a**–**b***; general procedure*

A mixture of (4*R* or 4*S*)-4-phenyl-oxazolidin-2-one (6.5 g, 41.4 mmol), *trans*-cinnamic acid (6.8 g, 46 mmol), and phosphorus oxychloride (13 mL) was heated at 70 °C for 2.5 h. The process was monitored by TLC. The reaction mixture was slowly cooled to room temperature and quenched by the addition of ice water (80 mL). Ice water (50 mL) was added again when the bubbles vanished, and the mixture was stirred at 0 °C for 1 h. The precipitate was filtered off and this crude product was purified by recrystallisation (ethyl acetate: hexane = 1 : 1) to give the pure product.

*(S)-4-Phenyl-3-((*E*)-3-phenylacryloyl)oxazolidin-2-one* (**1a**): White specula; yield 91%; m.p. 170–171.5 °C (lit.[23] 170 °C); $[\alpha]_D^{20}$=+0.8 (c 0.64, $CHCl_3$); ^{1}H NMR($CDCl_3$, 500 MHz) δ 7.96–7.27 (m, 12H, aromatic protons and –CH=CH–), 5.57 (q, J=3.8 Hz, 1H, oxazolidinone PhCH–), 4.74 (t, J=8.8 Hz, 1H, oxazolidinone –C$\underline{H}_2$), 4.32 (q, J=3.9 Hz, 1H, oxazolidinone –C$\underline{H}_2$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.2, 154.2, 147.1, 139.5, 134.9, 131.1, 129.6, 129.3, 129.1, 126.4, 117.3, 70.1, 58.3; IR (KBr) ν: 3080, 2987, 1774, 1681, 1624, 1390, 1332, 1226, 712 cm^{-1}; HRMS for $C_{18}H_{15}NO_3$: $[M+Na]^+$ (calcd.: 316.0944; Found: 316.0938).

*(*R*)-4-Phenyl-3-((*E*)-3-phenylacryloyl)oxazolidin-2-one* (**1b**): White specula; yield 92%; m.p. 169.2–170.9 °C (lit.[24] 172–174 °C); $[\alpha]_D^{20}$=–2.4 (c 0.60, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.95–7.26 (m, 12H, aromatic protons and –CH=CH–), 5.56 (q, J=3.9 Hz, 1H, oxazolidinone PhCH–), 4.75 (t, J=8.8 Hz, 1H, oxazolidinone –C$\underline{H}_2$), 4.32 (q, J=3.8 Hz, 1H, oxazolidinone –C$\underline{H}_2$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ:165.2, 154.2, 147.1, 139.5, 134.9, 131.1, 129.6, 129.3, 129.1, 129.0, 126.4, 117.3, 70.4, 58.3; IR (KBr) ν: 3080, 2987, 1773, 1681, 1624, 1390, 1332, 1212, 712 cm^{-1}; HRMS for $C_{18}H_{15}NO_3$: $[M+Na]^+$; calcd: 316.0944; found: 316.0946.

General procedure for the conjugate additions

A solution of **1a** or **1b** (3 g, 9.6 mmol) in 30 mL THF under N_2 was added dropwise to a mixture of freshly prepared cyclohexyl MgBr (19.2 mmol, 2 equiv.) and copper (I) bromide-dimethyl sufide complex (1 g, 4.8 mmol, 0.5 equiv.) in 50 mL THF at –78 °C. The resulting mixture was stirred at –78 °C for 15 min and 0 °C for 2 h, and then slowly warmed to room temperature for 1 h under N_2. The process was monitored by TLC and the reaction was quenched by addition of saturated ammonium chloride solution (20 mL) cautiously at 0 °C. The organic phase was separated and the aqueous layer was extracted by ether (2 × 20 mL). The combined organic extracts were washed with brine (2 × 30 mL) and water (30 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the crude product which was purified by silica gel chromatography (ethyl acetate: hexane = 1 : 15).

*(S)-3-((*R*)-3-Cyclohexyl-3-phenylpropanoyl)-4-phenyloxazolidin-2-one* (**2a**): White solid; yield 56%; m.p. 119.5–120.2 °C; $[\alpha]_D^{20}$=+92.2 (c 0.43, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.33–7.11 (m, 10H, aromatic protons), 5.15 (q, J=3.2 Hz, 1H, oxazolidinone, PhCH–), 4.43–4.40 (t, J=8.7 Hz, 1H, oxazolidinone, –CH_2), 4.15 (q, J=3.4 Hz, 1H, oxazolidinone, –CH_2); 3.52–3.47 (m, 1H, –C$_\beta\underline{H}$–), 3.24–3.19 (m, 1H, –C$_\alpha\underline{H}_2$–), 2.97–2.92 (m, 1H, –C$_\alpha\underline{H}_2$–), 1.79–0.52 (m, 11H, cyclohexyl proton); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.4, 154.1, 143.5, 139.4, 129.5, 129.0, 128.9, 128.7, 128.4, 126.6, 126.5, 125.3, 70.2, 58.0, 48.0, 43.3, 39.1, 31.4, 31.3, 26.8; IR (KBr) ν: 3035, 2923, 1784, 1701, 1450, 1391, 1387, 1240, 1172, 695 cm^{-1}; HRMS for $C_{24}H_{27}NO_3$: $[M+Na]^+$; calcd: 400.1883; found: 400.1880.

*(*R*)-3-((S)-3-Cyclohexyl-3-phenylpropanoyl)-4-phenyloxazolidin-2-one* (**2b**): White solid; yield 55%; m.p. 117.8–118.6 °C; $[\alpha]_D^{20}$=–99.5 (c 0.38, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37–7.12 (m, 10H, aromatic protons), 5.18 (q, J=3.4 Hz, 1H, oxazolidinone, PhCH–), 4.44 (t, J=8.7 Hz, 1H, oxazolidinone, –CH_2), 4.17 (q, J=3.5 Hz, 1H, oxazolidinone, –CH_2); 3.54–3.48 (m, 1H, –C$_\beta\underline{H}$–), 3.25–3.20 (m, 1H, –C$_\alpha\underline{H}_2$–), 2.98–2.94 (m, 1H, –C$_\alpha\underline{H}_2$–), 1.81–0.73 (m, 11H, cyclohexyl proton); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.4, 154.1, 143.5, 139.4, 129.5, 129.0, 128.9, 128.4, 126.6, 126.3, 125.6, 70.2, 58.0, 48.1, 43.3, 39.1, 31.4, 31.3, 26.7; IR (KBr) ν: 3035, 2922, 1785, 1702, 1451, 1390, 1327, 1214, 702 cm^{-1}; HRMS for $C_{24}H_{27}NO_3$: $[M+Na]^+$; calcd: 400.1883; found: 400.1876.

Direct azidation reaction; general procedure

CAUTION: Due to the possibility of explosion, the azides were handled with appropriate precautions at < 40 °C.

Potassium bis(trimethylsilyl)amide (KHMDS) (5 mL, 0.91 M in THF, 3 mmol, 1.5 equiv.) and NaH (280 mg, 60% in oil, 1.5 equiv.) was added using a syringe to a solution of **2a** or **2b** (800 mg, 2 mmol) in THF (15 mL) at −78 °C under N_2. The mixture was stirred at −78 °C under N_2 for 30 min. A precooled solution of trisyl azide (980 mg, 3 mmol, 1.5 equiv.) in THF (15 mL) was added *via* a cannula. The reaction mixture was stirred at −78 °C for 15 min and then quenched with acetic acid (1.75 mL, 9.2 mmol, 4.6 equiv.) and potassium acetate (30 mg, 0.3 mmol, 0.15 equiv.). The reaction flask was immediately immersed in a water bath at 35–40 °C for 10 h with stirring. The reaction was monitored by TLC and the reaction was quenched by addition of brine (20 mL). The organic phase was separated. The aqueous phase was extracted with ether (2 × 20 mL). The combined organic phases were washed with brine (2 × 20 mL) and water (2 × 20 mL), then dried over anhydrous $MgSO_4$. Removal of the solvents gave the crude product as a light yellow oil, which was purified by silica gel column chromatography (ethyl acetate : hexane = 1 : 15) to get the α-azido compound **3a** or **3b**.

*(S)-3-((2S,3*R*)-2-Azido-3-cyclohexyl-3-phenylpropanoyl)-4-phenyloxazolidin-2-one* (**3a**): yield 87%; white solid; m.p. 159–160 °C; $[\alpha]_D^{20}$=+225.3 (c 0.72, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.33–7.15 (m, 10H, aromatic protons), 5.66 (d, J=11.0 Hz, 1H, –C$_\alpha\underline{H}$–); 4.78–4.77. (m, 1H, oxazolidinone, PhCH–), 4.12 (t, J=8.4 Hz, 1H, oxazolidinone, –CH_2–), 4.06–4.03 (m, 1H, oxazolidinone, –CH_2–); 3.10–3.08 (m, 1H, –C$_\beta\underline{H}$–), 1.94–0.86 (m, 11H, cyclohexyl proton); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.9, 153.6, 138.6, 138.6, 129.9, 129.7, 129.2, 128.6, 127.6, 126.0, 70.4, 59.9, 58.1, 53.0, 39.8, 32.2, 29.1, 27.1, 26.8, 26.7; IR (KBr) ν: 3032, 2930, 2857, 2098, 1781, 1701, 1493,

1389, 1232, 1196, 707 cm^{-1}; HRMS for $C_{24}H_{26}N_4O_3$: [M+Na]$^+$ (calcd.: 441.1897; Found: 441.1893).

*(*R*)-3-((2*R*,3*S*)-2-Azido-3-cyclohexyl-3-phenylpropanoyl)-4-phenyloxazolidin-2-one* (**3b**): White solid; yield 86%; m.p. 162.1–162.5 °C; $[\alpha]_D^{20}$=–236.5 (c 0.59, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz,) δ 7.34–7.15 (m, 10H, aromatic protons), 5.66 (d, *J*=11.2 Hz, 1H, –C$_\alpha$H–); 4.79–4.77 (m, 1H, oxazolidinone, PhCH–), 4.12 (t, *J*=8.5 Hz, 1H, oxazolidinone, –CH$_2$–), 4.05 (q, *J*=2.8 Hz, *J*=8.6 Hz, 1H, oxazolidinone, –CH$_2$–); 3.10–3.07 (m, 1H, –C$_\beta$H–), 1.94–0.84 (m, 11H, cyclohexyl proton); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.9, 153.7, 138.6, 138.5, 129.9, 129.7, 129.2, 128.7, 127.7, 126.0, 70.4, 59.9, 58.1, 53.0, 39.8, 32.2, 29.0, 27.1, 26.9, 26.7; IR (KBr) *v*: 3032, 2930, 2857, 2098, 1781, 1701, 1494, 1390, 1232, 1196, 707 cm^{-1}; HRMS for $C_{24}H_{26}N_4O_3$: [M+Na]$^+$; calcd: 441.1897; found: 441.1895.

One-pot reduction and Boc protection of azido compounds; general procedure

A solution of azido compound **3a** or **3b** (1.8 g, 4.3 mmol) in ethyl acetate (40 mL) and Boc anhydride (1.9 g, 8.7 mmol) was placed in a flask with a balloon, and then 10% Pd/C (450 mg, 25%w) was added. The balloon was emptied and refilled with H_2 three times, and stirred under H_2 for 4 h. The catalyst was filtered off, and the volatile material was removed by rotary evaporation. The remaining material was purified by silica gel column chromatography (ethyl acetate : hexane = 1 : 10) to yield the compound **4a** or **4b**.

*tert-Butyl(1*R*,2*S*)-1-cyclohexyl-3-oxo-3-((*S*)-2-oxo-4-phenyl-oxazolidin-3-yl)-1-phenylpropan-2-ylcarbamate* (**4a**): White solid; yield 93%; m.p. 156.5–157 °C; $[\alpha]_D^{20}$=+99.5 (c 0.71, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27–7.08 (m, 10H, aromatic protons), 6.18 (t, *J*=9.8 Hz, 1H, –C$_\alpha$H–); 5.10 (s, 1H, –NH); 4.69 (t, *J*=5.4 Hz, 1H, oxazolidinone, PhCH–); 3.97 (d, *J*=7.2 Hz, 2H, oxazolidinone, –CH$_2$–); 2.81 (d, *J*=7.3 Hz, 1H, –C$_\beta$H–); 2.03–0.77 (m, 20H, cyclohexyl proton and –C(CH$_3$)$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.4, 155.3, 153.4, 138.9, 138.7, 130.3, 129.7, 129.5, 128.8, 128.3, 127.5, 126.3, 126.0, 80.4, 70.3, 58.1, 56.5, 54.0, 39.6, 39.2, 32.6, 29.1, 28.7, 27.5, 27.3, 27.1, 26.7; IR (KBr) *v*: 3357, 3251, 2979, 2929, 2857, 1782, 1705, 1522, 1455, 1380, 1254, 1184, 1043, 757, 708 cm^{-1}; HRMS for $C_{29}H_{36}N_2O_5$: [M+Na]$^+$; calcd: 515.2516; found: 515.2524.

*tert-Butyl(1*S*,2*R*)-1-cyclohexyl-3-oxo-3-((*R*)-2-oxo-4-phenyl-oxazolidin-3-yl)-1-phenylpropan-2-ylcarbamate* (**4b**): White solid; yield 91%; m.p. 156.2–157 °C; $[\alpha]_D^{20}$=–111.9 (c 0.46, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.25–7.07 (m, 10H, aromatic protons), 6.18 (t, *J*=9.9 Hz, 1H, –C$_\alpha$H–); 5.11 (s, 1H, –NH); 4.68 (d, *J*=4.2 Hz, 1H, oxazolidinone, PhCH–); 3.97 (d, *J*=7.3 Hz, 2H, oxazolidinone, –CH$_2$–); 2.81 (d, *J*=7.2 Hz, 1H, –C$_\beta$H–); 2.02–0.80 (m, 20H, cyclohexyl proton and –C(CH$_3$)$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.4, 155.4, 153.4, 138.9, 138.7, 130.3, 129.4, 128.8, 128.3, 127.6, 126.5, 126.0, 80.3, 70.3, 58.1, 56.4, 54.0, 39.6, 32.6, 29.1, 28.7, 27.2, 27.1, 26.7; IR (KBr) *v*: 3358, 3252, 2979, 2929, 2856, 1792, 1706, 1522, 1455, 1381, 1254, 1185, 1043, 757, 708 cm^{-1}; HRMS for $C_{29}H_{36}N_2O_5$: [M+Na]$^+$; calcd: 515.2516; found: 515.2509.

Hydrolysis of azido compounds; general procedure

Into a solution of α-azido compound **4a** or **4b** (600 mg, 0.6 mmol) in THF (40 mL), water was added (10 mL). After the solution was cooled at 0 °C for 15 min, 0.6 mL 30% hydrogen peroxide (3.6 mmol, 6 equiv.) was added dropwise, followed by the dropwise addition of 75 mg of lithium hydroxide monohydrate (1.8 mmol, 3 equiv.). The resulting mixture was stirred at 0 °C for 2.5 h. The reaction was quenched by the addition of saturated sodium sulfite (20 mL) and stirred at room temperature for 30 min. The aqueous phase was separated and extracted with ethyl acetate (3×20 mL) for recovery of the auxiliary, then the remaining aqueous phase was cooled to 0 °C and acidified with acetic acid, then extracted with ethyl acetate (3×20 mL). The combined organic phases were dried over anhydrous magnesium sulfate and after solvent removal under reduced pressure, purified by silica gel column chromatography (acetic acid : acetone : hexane = 2 : 1 : 40) to give **5a** or **5b** as a white solid.

*(2*S*,3*R*)-2-(tert-Butoxycarbonylamino)-3-cyclohexyl-3-phenyl-propanoic acid* (**5a**): White solid; yield 90%; m.p. 126.2–127.8 °C; $[\alpha]_D^{20}$=+0.70; (c 0.22, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10 (s, 1H, COOH), 7.33–7.12 (m, 5H, aromatic protons), 4.92–4.87 (m, 2H, –C$_\alpha$H– and –NH), 2.81–2.79 (m, 1H, –C$_\beta$H–), 2.24–0.75 (m, 20H, cyclohexyl proton and –C(CH$_3$)$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.1, 156.5, 140.2, 130.3, 129.7, 128.5, 81.4, 56.9, 55.7, 39.4, 32.8, 32.7, 29.7, 27.7, 27.5; IR (KBr) *v*: 3438, 3327, 2976, 2928, 2852, 2537, 1720, 1658, 1497, 1453, 1399, 1388, 1236, 1162, 1055, 1028, 771, 703 cm^{-1}; HRMS for $C_{20}H_{29}NO_4$: [M]$^+$; calcd: 347.2097; found: 347.2098.

*(2*R*,3*S*)-2-(tert-Butoxycarbonylamino)-3-cyclohexyl-3-phenyl-propanoic acid* (**5b**): White solid; yield 91%; m.p. 126.8–127.6 °C; $[\alpha]_D^{20}$=–0.74 (c 0.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.5 (s, 1H, COOH), 7.29–7.02 (m, 5H, aromatic protons), 4.89–4.87 (m, 2H, –C$_\alpha$H– and –NH), 2.78–2.76 (m, 1H, –C$_\beta$H–), 2.21–0.70 (m, 20H, cyclohexyl proton and –C(CH$_3$)$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.1, 155.5, 139.3, 129.4, 128.8, 127.6, 80.5, 56.0, 54.8, 38.5, 31.8, 28.8, 26.8, 26.6; IR (KBr) *v*: 3438, 3326, 2976, 2928, 2852, 2538, 1720, 1658, 1497, 1453, 1399, 1388, 1236, 1162, 1055, 1028, 772, 703 cm^{-1}; HRMS for $C_{20}H_{29}NO_4$: [M]$^+$; calcd: 347.2097; found: 347.2103.

Electronic Supplementary Information

The spectral data are available through: stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data.

This work was supported by National Natural Science Foundation of China (NSFC) (nos 21062009, 20562014), the Natural Science Foundation of Yunnan Province (no. 2011FZ059), and the Science and Technology Planning Project of Yunnan Province (no. KKSY201207140), which are gratefully acknowledged.

Received 12 September 2014; accepted 8 January 2015
Paper 1402880 doi: 10.3184/174751915X14219405044187
Published online: 13 February 2015

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