The synthesis of a chiral β-amino acid derivative by the Grignard reaction of an aspartic acid equivalent

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A novel synthetic route to chiral β-amino acid derivative has been developed by a Grignard reaction of 2,4,5-trifluorophenyl magnesium bromide with the Weinreb amide derivative of L-aspartic acid. The aspartic equivalent was synthesised from L-aspartic acid in four steps, and the Grignard reagent was prepared by Br–Mg-exchange reaction. The target compound was achieved after the Grignard reaction and a subsequent reduction. Tthe stereo structure of the chiral amine was well preserved from the L-aspartic acid.

Keywords: β-amino acid, aspartic acid, Grignard reaction

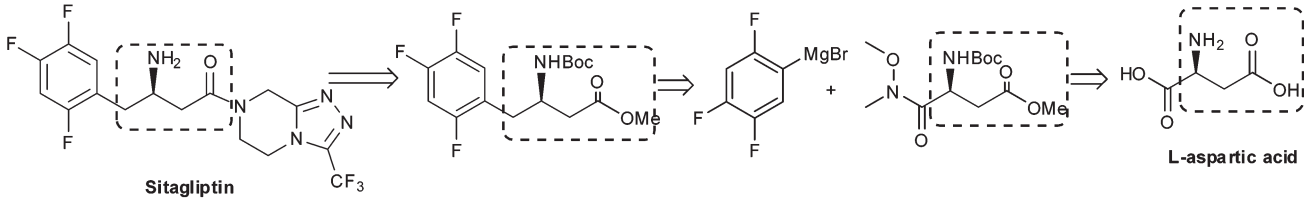
Enantiopure β-amino acids and their derivatives have found extensive application as components of numerous biologically active natural products as well as being important building blocks for the synthesis of β-peptides, β-lactam antibiotics and small molecule pharmaceuticals.[1–3] Consequently, developing new synthetic methods for the construction of β-amino acids and their derivatives has been important. Research has focused on facile, practical, and scalable methods for their preparation involving Arndt–Eistert homologation of the natural α-amino acid,[4] chemical and biological resolution,[5] chiral Lewis acid catalysed Mannich reaction,[6] asymmetric hydrogenation of enamino derivative,[7,8] asymmetric Michael addition of a chiral amine to an unsaturated ester,[9] modification of β-amino acid equivalent.[10–16] Given its inherent chiral efficiency and atom economy, the method that are based on β-amino acid equivalents potentially appears to be the most versatile.

Here, we report an approach to the enantiopure β-amino acid derivative, 3-R-Boc-amino-4-(2,4,5-trifluoro-phenyl) butyric acid methyl ester, a key synthetic intermediate of a new dipeptidyl peptidase IV (DPP-IV) inhibitor for the treatment of type 2 diabetes mellitus (T2DM), Sitagliptin. In this approach, the stereochemistry of the chiral amine is retained from the aspartic acid equivalent, which was synthesised from L-aspartic acid by a few steps (Scheme 1).

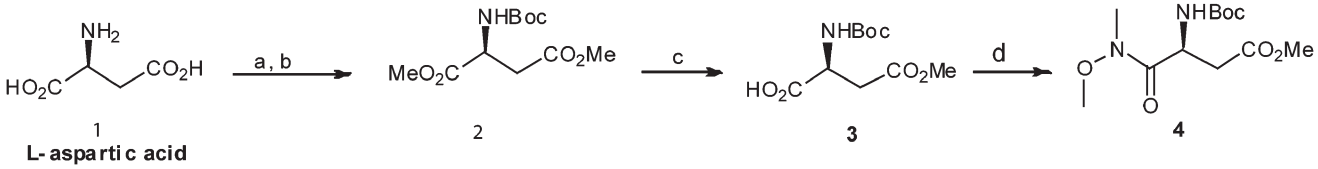
The synthetic work was initiated from L-aspartic acid **1** (Scheme **2**), which contains both α- and β-amino acid structural segment.

After di-methylation and Boc protection of the amine, the resultant compound **2** was selectively hydrolysed at the α-position with aq. LiOH in ethanol. In this process, the pH was controlled around 10 and the temperature was –10 °C. The mono acid **3** was condensed with N,O-dimethylhydroxylamine, to give the Weinreb amide, the β-amino acid equivalent **4** in 90% yield. The Grignard reaction was examined using 2,4,5-trifluoro-phenyl magnesium bromide. Since the direct reaction of Mg and 1-bromo-2,4,5-trifluoro- benzene will eliminate to yield benzyne and not the anticipated Grignard reagent, we used a bromine-magnesium-exchange reaction.[17] The Br–Mg-exchange of 1-bromo-2,4,5-trifluorobenzene was performed with *i*-PrMgBr at –20 °C in 1 h, monitored by GC at the point of disappearance of the bromobenzene (Scheme 3).

As the α-BOC-amino Weinreb amide **4** contains an exchangeable amino proton, excess Grignard reagent was required because the deprotonation of the exchangeable amino proton of **4** was faster than the nucleophilic attack at the Weinreb amide functional group.[18] The pre-deprotonation of the amino group was implemented by adding 1.0 equiv. of an inexpensive base *i*-PrMgBr at –10 °C, whose by-product propane is volatile and easily removed. This was followed by the addition of 1.1 equiv. of the nucleophile **6** at –20 °C. The α-Boc-amino ketone ester **7** was obtained in good yield. In this pre-deprotonation procedure, there was very little waste since only a small excess of the nucleophile was used. By minimising the



Scheme 1 Synthetic strategy of β-amino acid.



a) $SOCl_2$, MeOH, reflux. b) Boc_2O, Et_3N, CH_2Cl_2, r.t., 98 % for two step c) LiOH, EtOH-H_2O, –10 °C, 83 %.
d) isobutyl chloroformate, NMM, CH_2Cl_2, then N,O-dimethylhydroxylamine hydrochloride, –10 °C to r.t. 90 %.

Scheme 2

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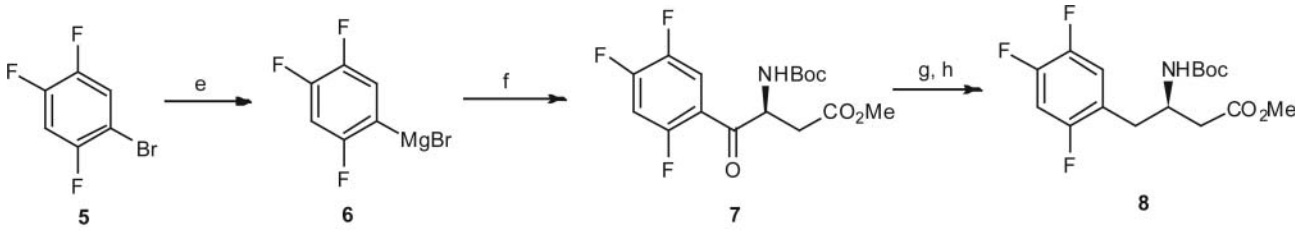

e) i-PrMgBr, THF, –20 °C. f) **4**, THF, –20 °C. 86 % g) Pd/C, 4atm H_2, HCl-Et_2O, r.t. h) Boc_2O, DCM, Et_3N, 75 % for two steps.

Scheme 3

formation of byproducts, purification of the desired ketone was made easier. This procedure is therefore more economical to run espercially in large scale production. The ketone **7** was reduced by Pd/C catalysed hydrogenation in absolute EtOH-ethereal HCl and the amine was again protected as the Boc derivative to give the target β-amino acid derivative **8**, 3-R-Boc-amino-4-(2,4,5-trifluoro- phenyl)butyric acid methyl ester in good yield.[19] The stereo configuration of compound **8** was confirmed after being compared with the reported data.[20]

In summary, we have developed a novel approach to synthesise the β-amino acid derivative, 3-R-Boc-amino-4-(2,4,5-trifluoro-phenyl)butyric acid methyl ester, by the Grignard reaction of aspartic acid equivalent. In this approach the stereo configuration of the chiral amine is retained from the aspartic acid equivalent. We hope that this discovery will provide a practical and efficient method for the preparation of β-amino acids and their derivatives. Further studies are currently underway in our laboratory.

Experimental

Melting points were determined with a SGW X-4 micro melting point apparatus. IR spectra were determined on a Bruker Vertex 70 spectrophotometer. ^{1}H NMR spectra were recorded using an Avance 400 MHz spectrometer. ESI-MS were recorded on Dionex MSOPlus Mass Spectrometer. High resolution mass spectra were recorded on Finnigan MAT XL95 mass spectrometer. GC were determined on Fuli GC-9790. Optical rotations were obtained on a Perkin-Elmer 241 Autopol polarimeter.

(S)-2-(Boc-amino)-4-methoxy-4-oxobutanoic acid (**3**):[21] To a solution of L-aspartic acid (26.6 g, 0.2 mol) in 150 mL methanol, thionyl chloride (25 g, 0.21 mol) was added dropwise at 0 °C. The mixture was then heated to reflux for 2 h and the cooled solvent was then removed under vacuum. The white solid residue was suspended on 200 mL of CH_2Cl_2 and Et_3N (45.5 g, 0.45 mol), Boc_2O (65.4 g, 0.3 mol) was added at room temperature. The mixture was stirred for 8 hours before water (200 mL) was added. The layers were separated, the organic layer was washed with sat. NaCl (200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to provide 51.2 g of crude **2** (98% for two steps). The crude product **2** was dissolved in 200 mL of EtOH at –10 °C, aq. LiOH(2N) was added to the mixture through the dropping funnel to maintain the pH = 10. The mixture was stirred until the point that TLC assay indicated complete consumption of ester starting material. Then the organic solvent was evaporated under reduced pressure below 40 °C, CH_2Cl_2 (200 mL) was added to the aqueous residue and stirred for 5 minutes, the organic layer was discarder. The aqueous layer was acidified with 1N HCl to pH = 3, then extracted with CH_2Cl_2 (2 × 150 mL). The combined organic layers were washed with sat. NaCl (200 mL), dried , filtered and concentrated to give the colourless viscous oil **3** (41.2 g, 0.167 mol), 83% yield. $[\alpha]_D^{20}$ = –18.5 (c 1.0, MeOH). IR (cm^{-1}): 2980, 1717, 1510, 1439, 1395, 1369, 1243, 1161, 1048, 1027, 844, 780, 738. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.85 (s, 1H), 5.61 (d, *J* = 8.3 Hz, 1H), 4.79–4.57 (m, 1H), 3.76 (s, 3H), 3.05 (d, *J* = 4.1 Hz, 1H), 2.87 (dd, *J* = 17.3, 4.5 Hz, 1H), 1.44 (s, 9 H). ESI-MS *m/z* 248.2(M + 1)$^+$.

(S)-methyl 3-(Boc-amino)-4-(methoxy(methyl)amino)-4-oxobutanoate (**4**):[22] Isobutylchlorocarbonate (4.08 g, 30 mmol) was added dropwise at –15 °C to a solution of **3** (7.41 g, 30 mmol) and N-methylmorpholine (6.5 mL, 60 mmol) in dichloromethane (100 mL). After stirring for 15 min 3.51 g (36 mmol) of N,O-dimethylhydroxylamine hydrochloride was added. The mixture was stirred for 1 h at –15 °C, then for 3 h at room temperature; 50 mL of water was added, the phases were separated, and the organic phase was dried with Mg_2SO_4 and concentrated. Flash chromatography with petroleum ether/ethyl acetate (l:l) resulted in 7.83 g (90%) of **4** as a colourless oil.[21] $[\alpha]_D^{20}$ = –20.5 (c 1.0, $CDCl_3$). IR (cm^{-1}): 3330, 2978, 1740, 1713, 1665, 1501, 1438, 1391, 1367, 1247, 1166, 1049, 1026, 989, 862, 826, 780, 735. ^{1}H NMR (400 MHz, DMSO) δ 5.39 (s, 1H), 5.01 (s, 1H), 3.79 (s, 3H), 3.70–3.67 (m, 3H), 3.22 (s, 3H), 2.77 (dd, *J* = 15.2, 5.7 Hz, 1H), 2.65 (d, *J* = 6.8 Hz, 1H), 1.38 (s, 9H). ESI-MS *m/z* 313.1(M + Na)$^+$.

(S)-methyl 3-(Boc-amino)-4-oxo-4-(2,4,5-trifluorophenyl)butanoate (**7**):[21] A dry three-necked flask equipped with a magnetic stirring bar and a N_2 balloon was charged with 1-bromo-2,4,5-trifluorobenzene (**5**; 4.62 g, 22 mmol) in THF (50 mL) and cooled to –20 °C, *i*-PrMgBr (22 mL, 22 mmol, 1 M in THF) was added dropwise and the reaction mixture was stirred at –20 °C for 1 h. At the point GC assay indicated disappearance of the bromobenzene, then the Grignard reagent **6** was stored as a THF solution in an inert gas atmosphere. α-BOC-amino Weinreb amide **4** (5.8 g, 20 mmol) was dissolved in 50 mL of dry THF, degassed and placed under N_2. The solution was cooled to –20 °C and to the resulting slurry was charged with 20 mL of 1.0 M *i*-PrMgBr/THF (20 mmol) dropwise at –15 to –5 °C to afford a clear solution. After cooling to –20 °C, the Grignard reagent **6** was exchanged above and added dropwise at ≤ 15 °C over 0.5 hour. The cooling bath was removed, and the mixture was allowed to warm to room temperature over 30 min. After a 4 h period at room temperature, the reaction was complete. The mixture was cooled in an ice bath and 100 mL of 1.0N HCl was added slowly at < 20 °C, followed by 100 mL of EtOAc. The aqueous layer was cut, and the organic layer was washed with 100 mL of water and dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded a pale yellow oil, after flash chromatography (silica gel, 3:1 hexane/EtOAc), 6.2 g of BOC-aminoacetophenone **7** was obtained as a colourless oil in 86% yield. $[\alpha]_D^{20}$ = –13.1 (c 1.0, $CDCl_3$). IR (cm^{-1}): 3371, 2977, 1710, 1625, 1512, 1427, 1368, 1336, 1291, 1250, 1215, 1163, 1051, 1027, 853, 801. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12–6.75 (m, 2H), 5.68 (d, *J* = 6.5 Hz, 1H), 5.15 (br, 1H), 3.71 (s, 3H), 3.15–2.97 (m, 1H), 2.88 (d, *J* = 11.0 Hz, 1H), 1.45 (s, 9H). ESI-MS *m/z* 384.1 (M + Na)$^+$. HRMS Calcd for $C_{16}H_{18}F_3NO_5Na$ (M + Na)$^+$ requires 384.1035, found 313.1043.

3-R-Boc-amino-4-(2,4,5-trifluoro-phenyl)butyric acid methyl ester (**8**): To a solution of **7** (6.2 g, 17.1 mmol) in EtOH (60 mL, absolute). Ethereal HCl (10 mL) and 1 g of 10% Pd/Cwas added. The mixture was shaken with H_2 (5 atm, 4 h), filtered, and evaporated to give a light yellow oil. 10% HCl (50 mL) and CH_2Cl_2 (50 mL) was added to the residue and stirred for 10 minutes, the organic layer was discarded. The aqueous layer was neutralised with K_2CO_3, then extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with sat. NaCl (50 mL), dried over anhyd. Na_2SO_4 and filtered. To this CH_2Cl_2 solution was added Et_3N (3.03 g, 30 mmol), Boc_2O (4.36 g, 20 mmol) at room temperature. The mixture was stirred for 8 hours before water (50 mL) was added, the layers were separated, the

organic layer was washed with sat. NaCl (50 mL), dried over anhyd. Na_2SO_4, filtered and concentrated to provide the crude product, recrystallised from toluene to give a pale yellow solid **8** (4.45 g, 12.8 mmol), 75% for two steps. $[\alpha]_D^{20} = +14.2$ (c 1.0, MeOH). M.p. 76–78 °C. {lit.[20] $[\alpha]_D^{20} = +15.2$ (c 1.0, MeOH). M.p. 88–88.5 °C.} IR (cm^{-1}): 3366, 2983, 1733, 1688, 1424, 1335, 1250, 1158, 1029, 838. ^1H NMR (400 MHz, $CDCl_3$) δ 7.17–6.72 (m, 2H), 5.18 (br, 1H), 4.18–4.00 (m, 1H), 3.72 (s, 3H), 2.92–2.85 (m, 2H), 2.58–2.47 (m, 2H), 1.37 (s, 9H). ESI-MS: 348.1 $(M + 1)^+$.

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