New Efficient Synthesis of β^2 -Amino Acid Derivatives by homologation of α -amino acids involving the Reformatsky reaction and Mannich Type Imminium Electrophile.

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Experimental procedure²²

General considerations

Tetrahydrofuran (THF) was distilled from sodium benzophenone and kept over 4 Å molecular sieves. Dichloromethane (CH₂Cl₂) and triethylamine (NEt₃) were distilled from CaH₂. Anhydrous methylal and other reagents were obtained from commercial suppliers and used without further purification. Anhydrous reaction were performed under argon atmosphere, glassware were dried in an oven prior to use. Protected amino acids and Oppolzer's sultam were a gift from Senn Chemicals. Prior to preparation of the HBr solution, the commercial concentrated HBr was washed with 5% solution of tributyl phosphate in CHCl₃ to remove contaminating Br₂. Reaction progress was monitored with TLC on precoated silica plates (Merck 60 F₂₅₄, 0.25 µm). The spots were detected by UV, molybdophosphoric acid oxidation or ninhydrin reagent. Flash column chromatography was carried out using Merck 60 F₂₅₄ 0.040-0.063 µm silica gel. ¹H and ¹³C NMR spectra were recorded on Bruker Avance 250 MHz or 400 MHz spectrometers. Chemical shifts (δ) are reported in ppm relative to internal TMS. Optical rotations were determined at 20°C on a Perkin-Elmer Model 141 polarimeter equipped with a 10 cm path length cell. Microanalyses were obtained from CNRS central service.

General Procedure for conversion of α-amino acids with non-functionalized side chain to α-bromoacids

To a stirred solution of L-Amino-Acid and sodium bromide (3.5 eq) in 2.5M H₂SO₄ (1.3 mL/mmol) was added drop wise at 0°C sodium nitrite (1.25 eq) in H₂O. After stirring for 1h at 0°C, the reaction was

brought to room temperature and stir for 6h. The mixture was extracted with ethyl acetate, and the combined organic solution was washed with brine, dried (MgSO_4), and concentrated *in vacuo*.

(S)-2-bromo-4-methyl-pentanoic acid 2b¹: From L-Leucine (20 g; 153 mmol) the crude product was purified by distillation under reduced pressure ($P = 0.03$ mm Hg, $T = 96^\circ\text{C}$) to give an oil (20.8 g; 70%); $[\alpha]_{\text{D}}^{20} -39.9$ (c 2, MeOH); NMR ^1H (400 MHz, CDCl_3): δ : 9.80-10.50 (*br s*, 1H); 4.30 (*t*, $J = 7.5$ Hz, 1H); 1.93 (*t*, $J = 7.5$ Hz, 2H); 1.76-1.90 (*m*, 1H); 0.98 (*d*, $J = 6.5$ Hz, 3H); 0.94 (*d*, $J = 6.25$ Hz, 3H); NMR ^{13}C (100 MHz, CDCl_3): δ : 176.4; 44.0; 43.2; 26.3; 22.3; 21.5

(S)-2-bromo-3-phenyl-propionic acid 2c²: From L-Phenylalanine (20g, 121.2 mmol) the crude product was purified by flash column chromatography (Cy/EA/AcOH, 99/1) to give an oil (19 g; 68%); $[\alpha]_{\text{D}}^{20} -11.4$ (c 2, MeOH); NMR ^1H (400 MHz, CDCl_3): δ : 7.18-7.36 (*m*, 5H); 4.42 (*t*, $J = 7.7$ Hz, 1H); 3.47 (*dd*, $J = 8$ Hz, 14.2 Hz, 1H); 3.24 (*dd*, $J = 7.2$ Hz, 14.2 Hz, 1H); NMR ^{13}C (100 MHz, CDCl_3): δ : 175.5; 136.3; 129.4; 129.0; 128.5; 127.5; 44.8; 40.7; Anal. calcd for $\text{C}_9\text{H}_9\text{BrO}_2$: C 47.19%, H 3.96%. Found: C 47.21%, H 3.60%

General Procedure for conversion of amino acids with functionalized side chain to the corresponding α -bromoacid

In a 3-necked flask with an overhead stirrer was dissolved NaBr (3.7 eq) in 0.75M aqueous solution of HBr. The solution was cooled to -15°C and sodium nitrite (1.3 eq) was added in one portion. The amino acid (1 eq) was then added and the reaction mixture was kept between -15°C and -10°C for 1.5 h. The mixture was extracted twice with precooled EtOAc (0°C). The combined organic layers were washed with saturated aqueous solution of NH_4Cl , dried (MgSO_4), and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

(S)-2-bromo-3- (N-tert-butoxycarbonylindoyl) propanoic acid 2d³: From H-Trp (Boc)-OH (5 g, 16.4 mmol) the crude product was purified by flash column chromatography (Cy/EA/AcOH, 7/3/0.1) to give compound **2d** as an oil (4 g, 67%); $[\alpha]_{\text{D}}^{20} -13.2$ (c 1, CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ : 8.87 (*br s*, 1H); 8.10 (*br s*, 1H); 7.51-7.53 (*m*, 2H); 7.32 (*t*, $J = 7.3$ Hz, 1H); 7.24 (*t*, $J = 6.8$ Hz, 1H); 4.52 (*t*, $J = 7.6$ Hz, 1H); 3.58 (*dd*, $J = 8.1$ Hz, 14.9 Hz, 1H); 2.93 (*dd*, $J = 6.8$ Hz, 14.9 Hz, 1H); 1.65 (*s*, 9H); ^{13}C NMR (100 MHz, CDCl_3): δ : 174.5; 149.6; 135.3; 129.7; 124.7; 124.5; 122.7; 118.5; 115.5; 115.4; 84.0; 43.3; 30.5; 28.2

(S)-2-bromo-4-tert-butylcarboxybutanoic acid 2e³: From H-Asp (OtBu)-OH (5 g, 26.4 mmol) the crude product was purified by flash column chromatography (Cy/EA/AcOH, 7/3/0.1) to give compound **2e** as an oil (11.5 g, 86%); $[\alpha]_D^{20} = -45.4^\circ$ (*c* 2, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ : 10.60 (*br s*, 1H); 4.55 (*dd*, *J* = 9.1 Hz, 6.1 Hz, 1H); 3.18 (*dd*, *J* = 9.1 Hz, 16.9 Hz, 1H); 2.93 (*dd*, *J* = 6.1 Hz, 16.9 Hz, 1H); 1.40 (*s*, 9H); ¹³C NMR (100 MHz, CDCl₃): δ : 174.8; 168.7; 82.5; 40.7; 38.1; 27.9; Anal. calcd for C₉H₁₃BrO₂: C 37.96%, H 5.18%. Found: C 37.70%, H 5.33%

Protection of the acid function for compounds with non-functionalized side chain

The α -bromoacid was treated with a solution of concentrated sulphuric acid (30 μ L/mmol) in methanol (2 mL/mmol) and refluxed for one hour. The solution was cooled to room temperature and concentrated *in vacuo*. Et₂O was added and the organic layer was washed with 5% aqueous solution of NaHCO₃ followed by brine, dried over MgSO₄ and concentrated *in vacuo*.

Methyl (S)-2-bromo-4-methyl-pentanoate 3b: Ester **3b** was purified by flash column chromatography (Cy-EA, 99/1) to give an oil (2.5 g, 79%); $[\alpha]_D^{20} = -49.6$ (*c* 1, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ : 4.29 (*t*, *J* = 7.6 Hz, 1H); 3.78 (*s*, 3H); 1.86-2.05 (*m*, 2H); 1.71-1.81 (*m*, 1H); 0.96 (*d*, *J* = 6.8 Hz, 3H); 0.91 (*d*, *J* = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ : 170.6; 52.9; 44.3; 43.5; 26.3; 22.3; 21.5

Methyl (S)-2-bromo-3-phenyl-propanoate 3c⁴: Ester **3c** was purified by flash column chromatography (Cy-EA, 99/1) to give an oil (6.8 g, 94%); $[\alpha]_D^{20} = -11.1$ (*c* 1, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ : 7.17-7.29 (*m*, 5H); 4.39 (*t*, *J* = 8.3 Hz, 1H); 3.36 (*s*, 3H); 3.45 (*dd*, *J* = 8.3 Hz, 14.1 Hz, 1H); 3.22 (*dd*, *J* = 7.1 Hz, 13.9 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ : 169.8; 136.7; 129.1; 128.6; 127.3; 52.8; 45.1; 41.0

Protection of the acid function for compounds with functionalized side chain

The α -bromoacid was treated with solution of acetyl chloride (30 μ L/mmol) in methanol (2 mL/mmol) for one hour. The solution was cooled to room temperature and concentrated *in vacuo*.

Methyl (S)-2-bromo-3-(N-tert-butoxycarbonylindoyl) propionate 3d: The crude product was purified by flash column chromatography (Cy/EA, 97/3) to give compound **3d** as an oil (1 g, 59%); $[\alpha]_D^{20}$

-18.6 (c 1, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ: 8.12-8.13 (*m*, 1H); 7.47-7.53 (*m*, 2H); 7.31-7.34 (*m*, 2H); 4.50 (*dd*, *J* = 8.6 Hz and 6.6 Hz, 1H); 3.73 (*s*, 3H); 3.58 (*dd*, *J* = 8.6 Hz, 14.9 Hz, 1H); 3.35 (*dd*, *J* = 6.6 Hz, 14.9 Hz, 1H); 1.66 (*s*, 9H); ¹³C NMR (100 MHz, CDCl₃): δ: 170.0; 150.0; 135.5; 129.7; 124.7; 124.5; 122.7; 118.6; 115.8; 115.4; 83.8; 53.0; 43.5; 30.8; 20.2; Anal. calcd for C₁₇H₂₀BrNO₄: C 53.42%, H 5.27%, N 3.66%. Found: C 53.00%, H 5.43%, N 3.27%

Methyl (S)-2-bromo-4-tert-butylcarboxybutanoate 3e: The crude product was purified by flash column chromatography (Cy/ EA, 97/3) to give compound **3e** as an oil (2.9 g, 51%); [α]_D²⁰ = -53.5 (c 1, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ: 4.53 (*dd*, *J* = 9.1 Hz, 6.1 Hz, 1H); 3.80 (*s*, 3H); 3.19 (*dd*, *J* = 9.1 Hz, 16.9 Hz, 1H); 2.91 (*dd*, *J* = 6.1 Hz, 16.9 Hz, 1H); 1.44 (*s*, 9H); ¹³C NMR (100 MHz, CDCl₃): δ: 169.7; 168.6; 82.0; 53.1; 40.9; 38.3; 27.9

Reformatsky reaction

Methyl N-(2-methyl-3-dibenzylaminomethyl) propionate 4a: The crude product was treated with 1% solution of TFA in EA, and purified by flash column chromatography (Cy/EA, 8/2 then Cy/EA/NEt₃, 8/2/0.1) to give **4a** as an oil (3 g, 43%); ¹H NMR (400 MHz, CDCl₃): δ: 7.19-7.30 (*m*, 10H); 3.62 (*d*, *J* = 13.4 Hz, 2H); 3.61 (*s*, 3H); 3.46 (*d*, *J* = 13.4 Hz, 2H); 2.73-2.70 (*m*, 2H); 2.37-2.44 (*m*, 1H); 1.07 (*d*, *J* = 6.3 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ: 176.1; 139.2; 128.9; 128.1; 126.9; 58.4; 57.3; 51.4; 38.6; 15.3; Anal. calcd for C₁₉H₂₃NO₂: C 76.73%, H 7.80%, N 4.71%. Found: C 76.87%, H 7.99%, N 4.65%

Methyl N- (2-dibenzylaminomethyl-4-methyl) pentanoate 4b: The crude product was treated with 1% solution of TFA in EA, and purified by flash column chromatography (Cy/EA, 8/2 then Cy/EA/NEt₃, 8/2/0.1) to give **4b** as an oil (4.8 g, 66%); ¹H NMR (400 MHz, CDCl₃): δ: 7.20-7.30 (*m*, 10H); 3.72 (*d*, *J* = 13.6 Hz, 2H); 3.63 (*s*, 3H); 3.36 (*d*, *J* = 13.6 Hz, 2H); 2.73-2.80 (*m*, 2H); 2.36-2.39 (*m*, 1H); 1.39-1.49 (*m*, 2H); 1.15-1.22 (*m*, 1H); 0.85 (*d*, *J* = 6.6 Hz, 3H); 0.82 (*d*, *J* = 6.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ: 175.9; 139.2; 128.9; 128.1; 126.9; 58.4; 56.8; 51.3; 42.9; 39.6; 26.3; 23.0; 22.0; Anal. calcd for C₂₂H₂₉NO₂: C 77.84%, H 8.61%, N 4.13%. Found: C 77.61%, H 8.73%, N 4.04%

Methyl N-(3-dibenzylamino-2-benzyl) propionate 4c: Compound **4c** (12.9 g; 53.1 mmol) was obtained after precipitation in MeOH-CHCl₃ as a white powder (14.6 g, 74%); mp = 83°C; ¹H NMR (400 MHz, CDCl₃): δ: 7.1-7.3 (*m*, 15H); 3.66 (*d*, *J* = 13.6 Hz, 2H); 3.42 (*d*, *J* = 13.6 Hz, 2H); 3.55 (*s*, 3H);

2.95-3.00 (*m*, 3H); 2.79-2.85 (*m*, 1H); 2.75-2.76 (*m*, 2H); 2.50-2.54 (*m*, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ : 174.9; 139.2; 139.0; 129.0; 128.7; 128.4; 128.2; 127.0; 126.3; 58.5; 55.9; 51.3; 46.9; 36.4; Anal. calcd for $\text{C}_{25}\text{H}_{27}\text{NO}_2$: C 80.40%, H 7.29%, N 3.75%. Found: C 80.16%, H 7.34%, N 3.67%

Methyl *N*-(2-dibenzyl-aminomethyl-3-(*N*-tert-butyloxycarbonylindoyl) propionate **4d:**

Compound **4d** (1.3 g; 3.4 mmol) was obtained after flash column chromatography (Cy/EA, 98/2) as an oil (14.6 g, 73%); ^1H NMR (400 MHz, CDCl_3): δ : 8.1 (*br s*, 1H); 7.43 (*d*, $J = 7.6$ Hz, 1H); 7.19-7.31 (*m*, 14H); 3.67 (*d*, $J = 13.6$ Hz, 2H); 3.45 (*d*, $J = 13.6$ Hz, 2H); 3.59 (*s*, 3H); 3.07-3.13 (*m*, 1H); 2.80-2.90 (*m*, 1H); 2.59 (*dd*, 1H, 5.8 Hz, 12.6 Hz); 1.65 (*s*, 9H); ^{13}C NMR (100 MHz, CDCl_3): δ : 175.1; 149.7; 138.0; 130.3; 128.9; 128.1; 127.0; 124.3; 123.1; 122.4; 118.8; 115.2; 83.4; 58.4; 56.0; 51.5; 44.8; 28.2; 25.7; DCI : $[\text{MH}^+] = 513, 413$ (M^+ -Boc)

Methyl *N*-(2-dibenzyl-aminomethyl-4-(*N*-tert-butyloxycarbonyl) butanoate **4e:**

Compound **4e** (1.2 g; 4.5 mmol) was obtained after flash column chromatography (Cy/EA, 97/3) as an oil (1.3 g, 72%); ^1H NMR (400 MHz, CDCl_3): δ : 7.2-7.4 (*m*, 10H); 3.59 (*d*, $J = 13.6$ Hz, 2H); 3.51 (*d*, $J = 13.6$ Hz, 2H); 3.3 (*s*, 3H); 3.0-3.1 (*m*, 1H); 2.7 (*dd*, $J = 7.3$ Hz, 10.2 Hz, 1H); 2.4-2.6 (*m*, 3H); 1.4 (*s*, 9H); ^{13}C NMR (100 MHz, CDCl_3): δ : 174.4; 171.2; 138.9; 128.9; 128.2; 127.0; 126.3; 80.7; 58.3; 55.1; 51.7; 40.5; 35.6; 28.0; Anal. calcd for $\text{C}_{24}\text{H}_{31}\text{NO}_4$: C 72.52%, H 7.86%, N 3.52%. Found: C 72.72%, H 7.89%, N 3.46%

Deprotection and Boc protection

To a solution of amine in a 1:4 mixture of THF-MeOH was added Pd/C 10% (100 mg/mmol) and ammonium formate (5 eq). The reaction mixture was stirred at room temperature. The solution was filtrated on a celite pad and concentrated. The amine was dissolved in a 1:1 mixture THF-water (5 mL/mmol). After addition of LiOH (2 eq), the mixture was stirred for 1-3h. After evaporation dioxane was added. After addition of Boc_2O (1.1 eq) and K_2CO_3 (1.1 eq), the solution was stirred for 5h and was then concentrated. After addition of water and extraction with Et_2O , the aqueous layer was cooled to 0°C, acidified to pH = 2 with HCl 1N and extracted with EA; the combined organic layers were dried and concentrated *in vacuo* leading to Boc-protected amino acid.

2- (*N*-Boc-aminomethyl) propionic acid **5a⁵:** Compound **5a** was purified by crystallization from ether-pentane (315 mg; 72%); mp = 89-90°C; NMR ^1H (400 MHz, CDCl_3): δ : 10.6 (*br s*, 1H); 6.43 and 5.08 (*br s*, 1H); 3.21-3.39 (*m*, 2H); 2.65-2.74 (*m*, 1H); 1.47 and 1.44 (*s*, 9H); 1.20 (*d*, $J = 7.5$ Hz, 3H);

NMR ^{13}C (100 MHz, CDCl_3): δ : 180.9; 179.6; 157.8; 156.1; 81.1; 79.6; 44.1; 42.7; 40.3; 40.0; 28.4; 14.6; Anal. calcd for $\text{C}_9\text{H}_{17}\text{NO}_4$: C 53.19%, H 8.43%, N 6.89%. Found: C 53.41%, H 8.42%, N 6.85%

2-(*N*-Boc-aminomethyl) 4-methyl pentanoic acid **5b⁵**: Compound **5b** was purified by crystallization from ether-pentane (152 g; 78%); mp = 74°C; ^1H NMR (400 MHz, CDCl_3): δ : 6.76 and 5.02 (*br s*, 1H); 3.32-3.41 (*m*, 1H); 3.19-3.26 and 3.00-3.07 (2*m*, 1H); 2.68-2.70 (*m*, 1H); 1.64-1.72 (*m*, 1H); 1.52-1.60 (*m*, 1H); 1.44-1.48 (2*s*, 9H); 1.19-1.35 (*m*, 3H); 0.96 (2*d*, J = 6.1 Hz and 6.6 Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ : 180.8 and 179.4; 155.9 and 158.1; 79.6 and 81.1; 43.7 and 44.1; 41.7 and 43.0; 38.6 and 39.0; 28.4; 25.8; 22.4; Anal. calcd for $\text{C}_{12}\text{H}_{23}\text{NO}_4$: C 58.75%, H 9.45%, N 5.71%. Found: C 58.84%, H 9.59%, N 5.61%

2-(*N*-Boc-aminomethyl) 3-phenyl propanoic acid **5c⁵**: Compound **5c** was purified by crystallization from ether-pentane (1.75 g, 80%); mp = 74°C; NMR ^1H (400 MHz, CDCl_3): δ : 9.65 (*br s*, 1H); 7.18-7.30 (*m*, 5H); 6.67 and 5.01 (*br s*, 1H); 3.37-3.41 (*m*, 0.5H); 3.22-3.27 (*m*, 1H); 2.80-3.11 (*m*, 3H); 2.63-2.72 (*m*, 0.5H); 1.37-1.42 (2*s*, 9H); NMR ^{13}C (100 MHz, CDCl_3): δ : 179.0 and 179.3; 155.9 and 158.0; 138.2; 138.1; 128.9; 128.8; 126.6; 79.7 and 81.2; 47.2 and 47.5; 41.2 and 42.0; 35.7 and 35.8; Anal. calcd for $\text{C}_{15}\text{H}_{21}\text{NO}_4$: C 64.50%, H 7.58%, N 5.01%. Found: C 64.19%, H 7.62%, N 4.90%

Asymmetric synthesis

(*S*)-*N*-(2-bromo-4-methyl-pentanoyl) camphorsultam **6**: To a stirred solution of (+)-10.2-camphorsultam (7.11 g, 33.3 mmol), in DME (90 mL), was added, at room temperature, NaH (1.47 g, 36.7 mmol). The solution was stirred for one hour. In parallel, to a solution of acid **2b** (6.5 g, 33.3 mmol) in DME (90 mL), was added, at -15°C, isobutyl chloroformate (4.8 mL, 36.7 mmol) and *N*-methylmorpholine (4 mL, 36.7 mmol). After 15 min stirring at -15°C, this preformed mixte anhydride was rapidly introduced, after filtration through a celite pad, over the sultam sodium salt's solution. After one hour stirring at -15°C and one hour at room temperature, the crude mixture was quenched with water and concentrated. After addition of EA, the solution was washed with saturated aqueous solution of NH_4Cl ; the organic layer was dried (MgSO_4) and concentrated. Compound **6** was purified by crystallization from ether-pentane as a white powder (8 g; 61%); mp = 132°C; $[\alpha]_{\text{D}}^{20}$ = 59.5 (*c* 1, CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ : 4.91 (*t*, J = 7.3 Hz, 1H); 3.93 (*dd*, J = 4.8 Hz, 7.3 Hz, 1H); 3.49 (*d*, J = 13.9 Hz, 2H); 3.39 (*d*, J = 13.9 Hz, 2H); 1.94-2.09 (*m*, 3H); 1.88-1.94 (*m*, 4H); 1.74 (*m*, 1H); 1.36-1.45 (*m*, 2H); 1.20 (*s*,

3H); 0.98 (*s*, 3H); 0.97 (*d*, *J* = 6.8 Hz, 3H); 0.92 (*d*, *J* = 6.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ: 168.3; 64.9; 53.0; 48.7; 47.9; 44.5; 43.7; 42.4; 37.5; 32.7; 26.5; 26.4; 22.4; 22.0; 20.7 and 19.9; Anal. calcd for C₁₆H₂₆NO₃SBr: C 48.98%, H 6.68%, N 3.57%. Found: C 48.60%, H 6.72%, N 3.53%

2-(*R*)-(N-Boc-aminomethyl) 4-methyl-pentanoic acid 8⁵: Following the procedure described for compounds **5a-c**, compound **8** was obtained by crystallization from ether-pentane (2.3 g; 80%); mp = 74°C; [α]_D²⁰ −3.1 (*c* 1, CHCl₃); NMR: in accordance with compound **5b**

^1H and ^{13}C NMR spectra (400MHz, CDCl_3) for compound 4a

^1H and ^{13}C NMR spectra (400MHz, CDCl_3) for compound 4b

^1H and ^{13}C NMR spectra (400MHz, CDCl_3) for compound 4c

^1H and ^{13}C NMR spectra (400MHz, CDCl_3) for compound 4d

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^1H and ^{13}C NMR spectra (400MHz, CDCl_3) for compound 4e

^1H and ^{13}C NMR spectra (400MHz, CDCl_3) for compound 7

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