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The synthesis of Fmoc-*O*-allyl β-serine

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ABSTRACT

Two concise routes for the synthesis of the title amino acid have been developed. The first route employs Seebach's general approach [Seebach, D.; Lelais, G.; Micuch, P.; Josien-Lefebvre, D.; Rossi, F. *Helv. Chim. Acta* **2004**, *87*, 3131] with Arndt Eistert homologation of Boc-*O*-allyl α-serine as the key process. The second route employs an approach using Boc-α-aspartic acid as a starting material [Salzmann, T.N.; Ratcliffe, R.W.; Christensen, B.G.; Bouffard, F.A. *J. Am. Chem. Soc.* **1980**, *102*, 6163; Rodriguez, M.; Llinares, M.; Doulut, S.; Heitz, A.; Martinez, J. *Tetrahedron. Lett.* **1991**, *32*, 923] with a selective palladium-catalysed O-allylation [Haight, A.R; Stoner, E.J.; Peterson, M.J.; Grover, V.K. *J. Org. Chem.* **2003**, *68*, 8092] as key processes. These two routes are evaluated for their relative efficiency and safety.

1. Introduction

As part of a programme directed towards the synthesis of new materials based on stapled β-peptides,[5] we required β-amino acid, Fmoc-*O*-allyl-β-serine **1**. This amino acid has not been reported previously. Of the many approaches to the synthesis of enantiomerically pure β-amino acids, those of Seebach[1] and Salzmann (in the context of β-lactams)[2] appeared applicable. Each will be discussed in turn (see Fig. 1).

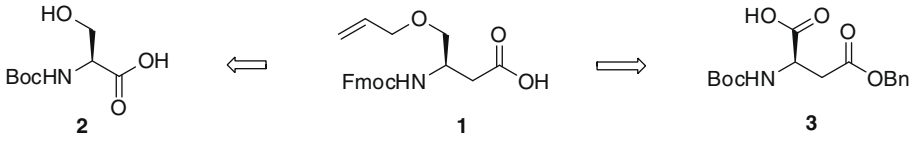
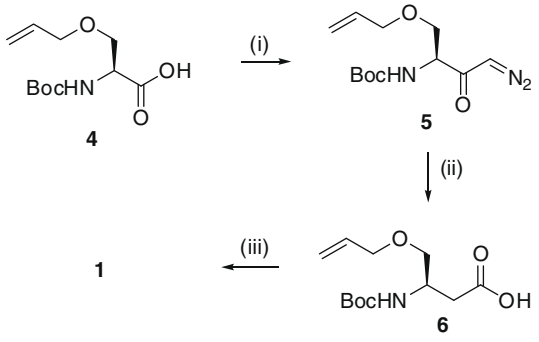


Figure 1.

2. Results and discussion

Seebach's general approach to the synthesis of β-amino acids involves Arndt Eistert homologation[1] of the corresponding α-amino acid (Scheme 1). In our case, the corresponding α-amino acid, Boc-*O*-allyl-α-serine **4,** was a known compound.[6] Treatment of **4** with triethylamine and ethyl chloroformate generated the mixed anhydride, which was then reacted with diazomethane to give diazoketone **5** in excellent yield. Silver-catalysed rearrangement then provided the new β-amino acid, Boc-*O*-allyl-β-serine **6**, again in almost quantitative yield. Removal of the Boc group was best effected by employing TFA in DCM. Reprotection with Fmoc–OSu thus provided the target compound **1** in 62% overall yield from **2**.

In order to avoid the use of the hazardous diazomethane, especially for larger-scale work, we explored the use of TMS-diazomethane[7] as a safer alternative. However, yields with this



Scheme 1. Reagents and conditions: (i) $ClCO_2Et$, Et_3N, THF, −25 °C to rt, o/n (ii) CF_3CO_2Ag, Et_3N, THF/H_2O, −25 °C to rt, o/n (iii) (a) TFA, DCM, rt, 1 h; (b) Na_2CO_3, FmocOSu, acetone, rt, o/n.

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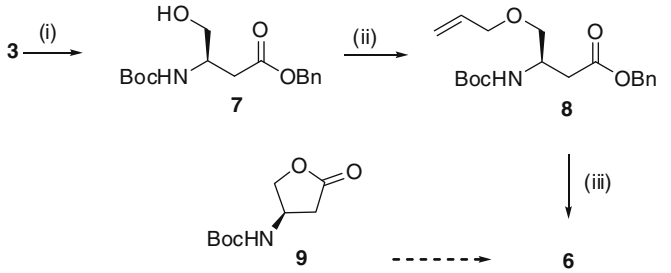
reagent were consistently poor giving, at best, approximately 25% yields for the conversion of **4** to **5**.

The second route takes advantage of the selective transformation of the α-carboxylic acid in partially protected aspartate **3**, yielding alcohol **7** in good yield (Scheme 2).[2,3] Initial attempts to allylate the hydroxyl group with allyl bromide and sodium hydride gave lactone **9**[8] as the main product. Switching to palladium-catalysed allylation[4] with allyl ethyl carbonate somewhat depressed production of lactone **9** providing the *O*-allyl product **8** in 42% isolated yield. Ester hydrolysis then produced **6,** which as we have shown above could be converted into the desired target in two steps. In principle, hydrolysis of lactone **9** should provide **6**; however, this has yet to be investigated.



Scheme 2. Reagents and conditions: (i) (a) $ClCO_2t$-Bu, NMM, DME, −10 °C, 10 min; (b) $NaBH_4$, H_2O, 0 °C, 1 min (ii) allyl ethyl carbonate, $Pd(Ph_3P)_4$, THF, 40 °C, 1 h (iii). LiOH (aq.), THF/MeOH, rt, o/n.

3. Conclusions

In conclusion, we have developed and evaluated two practical routes to the new β-amino acid, Fmoc-*O*-allyl-β-serine **1**. Although the second route suffers from losses in the allylation step, it is the preferred route for scale-up as it avoids the use of hazardous diazomethane.

4. Experimental

4.1. General

If dry and air-free conditions were required, reactions were performed in oven-dried glassware (120 °C) under a positive pressure of nitrogen or argon. NMR spectra were recorded on a Varian 300 or 500 spectrometer or a Bruker AM 300 or Bruker Advance DRX 400 spectrometer. Infrared spectra were recorded on a Perkin Elmer 1600 Series Fourier Transform spectrometer. High resolution mass spectra (HRMS) were recorded on a Bruker BioApex 47e FTMS. Melting points were recorded on an electrothermal melting point apparatus and are uncorrected.

Silica gel used for flash chromatography was 40–63 μm (230–400 mesh) silica gel 60 (Merck No. 9385). Dichloromethane (DCM) was distilled from P_2O_5. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl prior to use. Dimethylformamide (DMF) was dried over 4 Å molecular sieves. All other solvents were used as supplied. Commercially available reagents were used without further purification.

4.1.1. (*S*)-*tert*-Butyl 1-(allyloxy)-4-diazo-3-oxobutan-2-ylcarbamate 5

Boc-L-allyl serine **4**[6] (100 mg, 0.41 mmol) was dissolved in THF (2 mL) under an atmosphere of nitrogen and was cooled to −25 °C. The *N*-methylmorpholine (47 μL, 0.43 mmol) and ethyl chloroformate (41 μL, 0.43 mmol) were added dropwise, and the resulting mixture was stirred at this temperature for 1 h. The reaction was allowed to warm to 0 °C, and diazomethane (generated in situ) was bubbled across to the reaction flask. Once consumption of diazald was noted, the reaction was allowed to warm to room temperature and stirred overnight. Excess diazomethane was quenched by the addition of acetic acid (a few drops) while stirring. The reaction mixture was diluted with diethyl ether, washed with a saturated aqueous $NaHCO_3$ solution, saturated aqueous NH_4Cl and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give the crude product, which was purified by flash chromatography (1:1 ethyl acetate:hexanes) to afford **5** (100 mg, 91%) as a colourless oil.

4.1.2. Alternative procedure

Boc-L-allyl serine **4** (153 mg, 0.62 mmol) was dissolved in THF (3 mL) under an atmosphere of nitrogen and was cooled to −25 °C. Triethylamine (91 μL, 0.65 mmol) and ethyl chloroformate (63 μL, 0.65 mmol) were added dropwise, and the resulting mixture was stirred at this temperature for 1 h. The reaction was allowed to warm to 0 °C, and a 2.0 M solution of (trimethylsilyl)-diazomethane in diethyl ether (620 μL, 1.24 mmol) was added. The resulting yellow solution was allowed to warm to room temperature overnight. The reaction mixture was diluted with diethyl ether, washed with a saturated aqueous $NaHCO_3$ solution, saturated aqueous NH_4Cl and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give the crude product, which was purified by flash chromatography (1:1 ethyl acetate:hexanes) to afford the product (40 mg, 24%) as a colourless oil.

$[\alpha]_D^{20} = -12.0$ (*c* 1.0, $CHCl_3$). IR (CH_2Cl_2) *ν* 3436, 2981, 2863, 2253, 2113, 1794, 1710, 1640, 1497, 1366, 1251, 1163 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) *δ* (ppm): 1.46 (s, 9H), 3.55 (dd, *J* = 9.5, 5.2 Hz, 1H), 3.82 (dd, *J* = 9.4, 3.6 Hz, 1H), 3.96–4.00 (m, 2H), 4.29 (br s, 1H), 5.19 (dq, *J* = 10.3, 2.7, 1.2 Hz, 1H), 5.25 (dq, *J* = 17.2, 3.2, 1.5 Hz, 1H), 5.39 (m, 1H), 5.57 (br s, 1H), 5.85 (ddt, *J* = 17.1, 10.4, 5.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* (ppm): 28.6, 54.4, 58.0, 69.9, 72.6, 80.5, 117.8, 134.3, 155.7, 193.2. HRMS (ESI) *m/z*: calcd mass for $C_{12}H_{19}N_3NaO_4$: 292.1273. Found: 292.1270.

4.2. (*R*)-4-(Allyloxy)-3-(*tert*-butoxycarbonylamino)butanoic acid 6

To a solution of diazoketone **5** (105 mg, 0.39 mmol) in THF (1 mL) and water (1 mL), under an atmosphere of nitrogen and protected from light, was added a solution of silver trifluoroacetate (17 mg, 0.078 mmol) in triethylamine (136 μL, 0.795 mmol) at −25 °C. The reaction was allowed to warm to room temperature and stirred overnight. Volatiles were removed in vacuo and saturated aqueous $NaHCO_3$ was added, and the resulting solution was stirred for 1 h. The aqueous solution was extracted with diethyl ether, acidified to pH 2 with the addition of 1 M aqueous HCl and extracted twice with ethyl acetate. The combined organics were washed with brine, dried over $MgSO_4$ and concentrated in vacuo to afford the product (81 mg, 80%) as a pale yellow oil, which was utilised in the next step without further purification.

$[\alpha]_D^{20} = +11.0$ (*c* 1.0, $CHCl_3$). IR (neat) *ν* 3083, 2979, 2932, 1710, 1509, 1394, 1368, 1283, 1242, 1158 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) *δ* (ppm): 1.44 (s, 9H), 2.67 (m, 2H), 3.49 (dd, *J* = 9.6, 5.3 Hz, 1H), 3.54 (dd, *J* = 9.5, 4.2 Hz, 1H), 3.92–4.04 (m, 2H), 4.12 (m, 1H), 5.14 (br s, 1H), 5.18 (dq, *J* = 10.4, 2.9, 1.3 Hz, 1H), 5.26 (dq, *J* = 17.3, 3.3, 1.6 Hz, 1H), 5.87 (ddt, 17.2, 10.4, 5.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) *δ* (ppm): 28.5, 36.3, 47.3, 71.0, 72.3, 79.9, 117.4, 134.5, 155.6, 176.4. HRMS (ESI) *m/z*: calcd mass for $C_{12}H_{21}NNaO_5$: 282.1317. Found: 282.1314.

4.3. (*R*)-4-(Allyloxy)-3-aminobutanoic acid, trifluoroacetic acid salt 10

To a solution of the above crude **6** (2.70 g, 10.41 mmol) in CH_2Cl_2 (145 mL) was added trifluoroacetic acid (73 mL) at 0 °C.

The reaction was stirred for 1 h at room temperature, concentrated in vacuo and freeze dried overnight to afford the trifluoroacetic acid salt (2.59 g, 91%) as a pale orange oil. $[\alpha]_D^{20} = +3.0$ (*c* 1.0, $CHCl_3$). IR (neat) *ν* 2924, 1674, 1505, 1479, 1426, 1267, 1202, 1140 cm^{-1}. ^1H NMR (300 MHz, MeOD) *δ* (ppm): 2.67–2.83 (m, 2H), 3.59 (dd, *J* = 10.2, 6.1 Hz, 1H), 3.67–3.77 (m, 2H), 4.04–4.14 (m, 2H), 5.24 (dm, *J* = 10.4 Hz, 1H), 5.34 (dm, *J* = 17.3 Hz, 1H), 5.96 (m, 1H). ^{13}C NMR (75 MHz, MeOD) *δ* (ppm): 34.7, 49.6, 69.9, 73.5, 118.3, 135.4, 173.4. HRMS (ESI) *m/z*: calcd mass for $C_7H_{14}NO_3$: 160.0974. Found: 160.0969.

4.4. (*R*)-3-(((9*H*-Fluoren-9-yl)methoxy)carbonylamino)-4-(allyloxy)butanoic acid 1

To the amine salt **10** (2.50 g, 9.15 mmol), a 10% aqueous solution of Na_2CO_3 was added until the pH of the resulting solution was 10. It was cooled to 0 °C, and Fmoc–OSu (3.70 g, 10.98 mmol) in acetone (115 mL) was added. The reaction was stirred at room temperature overnight. Volatiles were removed in vacuo, and the resulting aqueous solution was diluted with water and ethyl acetate. The layers were separated, and the aqueous layer was acidified to pH 2 with the addition of 2 M aqueous HCl and extracted twice with ethyl acetate. The combined organics were washed with brine, dried over Na_2SO_4 and concentrated in vacuo to afford a pale yellow oil. The oil was lyophilised from acetonitrile/water (50:50) to afford **1** (3.35 g, 96%) as an off-white solid. Mp 69–71 °C. $[\alpha]_D^{20} = +11.0$ (*c* 1.0, $CHCl_3$). IR (neat) *ν* 3322, 3018, 1710, 1517, 1450, 1219 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) *δ* (ppm): 2.69 (m, 2H), 3.55 (m, 2H), 3.98 (m, 2H), 4.22 (m, 2H), 4.40 (m, 2H), 5.19 (dd, *J* = 10.4, 1.0 Hz, 1H), 5.25 (d, *J* = 17.3 Hz, 1H), 5.41 (bd, *J* = 6.8 Hz, 1H), 5.87 (m, 1H), 7.31 (dt, *J* = 7.4, 1.2 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 2H), 7.58 (d, *J* = 7.3 Hz, 2H), 7.75 (d, *J* = 7.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) *δ* (ppm): 36.1, 47.4, 47.9, 67.1, 70.8, 72.3, 117.5, 120.1, 125.2, 127.2, 127.8, 134.3, 141.5, 144.0, 156.1, 176.4. HRMS (ESI) *m/z*: calcd mass for $C_{22}H_{23}NNaO_5$: 404.1474. Found: 404.1472.

4.5. (*R*)-Benzyl 3-(*tert*-butoxycarbonylamino)-4-hydroxybutanoate 7

To a stirred solution of Boc-D-aspartic acid 4-benzyl ester **3** (5.00 g, 15.47 mmol) in DME (15 ml) were added *N*-methylmorpholine (1.70 mL, 15.47 mmol) and isobutyl chloroformate (2.02 mL, 15.47 mmol) at −10 °C. Upon stirring at this temperature for 10 min, the precipitated *N*-methyl morpholine hydrochloride salt was removed by filtration and the solid was washed with DME. The combined filtrate was placed in a large conical flask and was cooled to 0 °C, and a solution of $NaBH_4$ (0.88 g, 23.26 mmol) in water (8 mL) was added in one portion resulting in evolution of gas. Additional water (400 mL) was added immediately afterwards and the product precipitated out of solution. Ethyl acetate was added, the layers were separated, and the organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The resulting oily residue was freeze dried overnight to afford the product (4.54 g, 95%) as a white solid, which was utilised in the next step without further purification. Mp 62–64 °C. $[\alpha]_D^{20} = -14.0$ (*c* 1.0, $CHCl_3$). IR (neat) *ν* 3400, 2978, 1693, 1512, 1456, 1392, 1367, 1250, 1168 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) *δ* (ppm): 1.43 (s, 9H), 2.61 (br s, 1H), 2.63–2.70 (m, 2H), 3.68 (s, 1H), 3.69 (s, 1H), 4.00 (m, 1H), 5.13 (s, 2H), 5.20 (br s, 1H), 7.30–7.38 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* (ppm): 28.4, 36.1, 49.5, 64.6, 66.7, 79.9, 128.3, 128.4, 128.6, 135.6, 155.8, 171.6. HRMS (ESI) *m/z*: calcd mass for $C_{16}H_{23}NNaO_5$: 332.1474. Found: 332.1474.

4.6. (*R*)-Benzyl 4-(allyloxy)-3-(*tert*-butoxycarbonylamino)-butanoate 8

Alcohol **7** (5.00 g, 16.16 mmol) was dissolved in degassed (argon), dry THF (100 mL) under an atmosphere of argon. Allyl ethyl carbonate (2.94 mL, 22.63 mmol) and $Pd(Ph_3P)_4$ (375 mg, 0.32 mmol) were added to the stirring solution. The system was degassed (argon) for a few minutes, heated to 40 °C and stirred at this temperature for 1 h. The solution was concentrated in vacuo, and the resulting residue was purified by flash chromatography (1:4 ethyl acetate:hexanes) to afford desired product **8** as a viscous, pale yellow oil (2.37 g, 42%). Lactone **9** (1.46 g, 45%) was also obtained as an off-white crystalline solid. $[\alpha]_D^{20} = +8.0$ (*c* 1.0, $CHCl_3$). IR (neat) *ν* 3370, 2978, 1715, 1500, 1456, 1366, 1247 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) *δ* (ppm): 1.43 (s, 9H), 2.62–2.70 (m, 2H), 3.46 (dd, *J* = 9.4, 5.2 Hz, 1H), 3.51 (dd, *J* = 9.5, 4.1 Hz, 1H), 3.88–3.98 (m, 2H), 4.14 (m, 1H), 5.12 (s, 2H), 5.13 (br s, 1H), 5.15 (dq, *J* = 10.4, 3.0, 1.3 Hz, 1H), 5.22 (dq, *J* = 17.2, 3.3, 1.8 Hz, 1H), 5.84 (ddt, 17.2, 10.4, 5.6 Hz, 1H), 7.29–7.37 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* (ppm): 28.3, 36.4, 47.5, 66.4, 71.0, 72.1, 79.4, 117.0, 128.2, 128.4, 128.6, 134.5, 136.0, 155.2, 171.3. HRMS (ESI) *m/z*: calcd mass for $C_{19}H_{27}NNaO_5$: 372.1787. Found: 372.1780.

4.7. (*R*)-*tert*-Butyl 5-oxotetrahydrofuran-3-ylcarbamate 9

Mp 113–115 °C. $[\alpha]_D^{20} = +56.0$ (*c* 1.0, $CHCl_3$). IR (neat) *ν* 3357, 2981, 2931, 1781, 1700, 1507, 1457, 1369, 1253, 1169 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) *δ* (ppm): 1.44 (s, 9H), 2.44 (dd, *J* = 18.0, 4.2 Hz, 1H), 2.82 (dd, *J* = 17.9, 7.7 Hz, 1H), 4.20 (dd, *J* = 9.1, 2.8 Hz, 1H), 4.45 (m, 1H), 4.49 (dd, *J* = 10.9, 5.9 Hz, 1H), 4.95 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) *δ* (ppm): 28.4, 35.2, 47.9, 73.8, 80.8, 155.2, 175.1. HRMS (ESI) *m/z*: calcd mass for $C_9H_{15}NNaO_4$: 224.0899. Found: 224.0894.

4.8. (*R*)-4-(Allyloxy)-3-(*tert*-butoxycarbonylamino)butanoic acid 6

Benzyl ester **8** (3.60 g, 10.30 mmol) was dissolved in THF (90 mL) and methanol (9 mL) under an atmosphere of nitrogen and was cooled to 0 °C. An aqueous solution of LiOH (69 mL, 1.5 M, 103.0 mmol) was added slowly, and the reaction mixture was stirred at room temperature overnight. Volatiles were removed in vacuo, and water and ethyl acetate were added. The layers were separated, and the aqueous layer was acidified to pH 2 with the addition of 2 M aqueous HCl and extracted twice with ethyl acetate. The combined organics were washed with brine, dried over Na_2SO_4 and concentrated in vacuo to afford the product (2.54 g, 98%) as a pale yellow oil.

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