Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 6079–6082

TETRAHEDRON LETTERS

Synthesis of (*R*) and (*S*) enantiomers of Fmoc-protected 1,2,4-oxadiazole-containing β³-amino acids from Fmoc-(*R*)-β-HAsp(O*t*Bu)-OH

Abdallah Hamzé, Jean-François Hernandez* and Jean Martinez

Laboratoire des Aminoacides Peptides et Protéines, CNRS UMR 5810, Universités Montpellier I et II, Faculté de Pharmacie, 15 avenue Charles Flahault, BP 14491, 34093 Montpellier cedex 5, France

Received 29 April 2003; revised 12 June 2003; accepted 12 June 2003

Abstract—Fmoc-(*R*)-β-HomoAsp(O*t*Bu)-OH was used for the synthesis of both (*R*) and (*S*) enantiomers of various Fmoc-protected 3-substituted 1,2,4-oxadiazole-containing β³-amino acids. The 1,2,4-oxadiazole heterocycle was formed using sodium acetate, a Fmoc-compatible and efficient catalyst for cyclodehydration.

β-Amino acids have received increasing attention in the last years. Several reasons account for such an interest, including their occurrence in natural compounds with very interesting pharmacological properties,[1–4] as well as their usefulness in the design of peptidomimetics. β-Peptides, polymers constituted uniquely with β³-amino acids, have been shown to adopt new stable well-ordered secondary structures.[5–9] Substitution of at least one α-amino acid for its β³ isomer in a peptide sequence has also been reported. In that case, the additional methylene group(s) might impair molecular recognition by the target by steric hindrance and/or local conformational disruption, especially when introduced in a turn. Nevertheless, this modification if tolerated represents an interesting approach to provide peptides with increased enzymatic stability.[10–13]

We have been interested in the development of new Fmoc-protected chiral β-amino acids which could be used as building blocks in the combinatorial synthesis of pharmacologically active peptide analogs or protease inhibitors. Recently, we focused our attention on the synthesis of 1,2,4-oxadiazole-containing amino acids.[14] This heterocycle[15–17] has been frequently used as ester or amide bioisostere[18–20] and can help with the design of compounds with improved physico-chemical properties and bioavailability.[21] 1,2,4-Oxadiazoles are commonly synthesized from amidoximes and carboxylic acid derivatives in two steps.[15–17] During the first step, a diversely substituted amidoxime is *O*-acylated by an activated carboxylic acid derivative (here a conveniently protected amino acid). The heterocycle is subsequently formed by intramolecular cyclo-dehydration. It can thus be afforded with a large variety of substituents in position 3, the amino acyl-derived moiety being branched on position 5.

β³-Amino acids are efficiently prepared using Arndt–Eistert homologation of α-amino acid derivatives.[22] This method proceeds stereospecifically to a high degree in most cases and suitable conditions have been found for a variety of Nα-protecting groups, including Fmoc.[23–25] Each enantiomer is obtained from the corresponding α-amino acid derivative.

Here, we report the synthesis of Fmoc-protected 1,2,4-oxadiazole-containing β³-amino acids, following

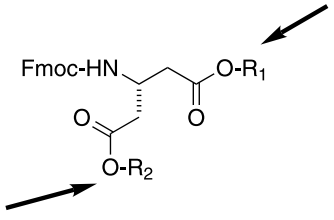


Figure 1. Fmoc-β-HAsp derivative precursors of the *R* enantiomer (R_1 = H, R_2 = *t*-Bu) and the *S* enantiomer (R_1 = Allyl, R_2 = H) of Fmoc-protected 1,2,4-oxadiazole-containing β³-amino acids. The oxadiazole ring can be built on anyone of the two carboxylic groups.

Keywords: β³-amino acid; 1,2,4-oxadiazole; Fmoc.
* Corresponding author. Tel.: 33-(0)4 67 54 86 62; fax: 33-(0)4 67 54 86 54; e-mail: hernandez@colombes.pharma.univ-montp1.fr

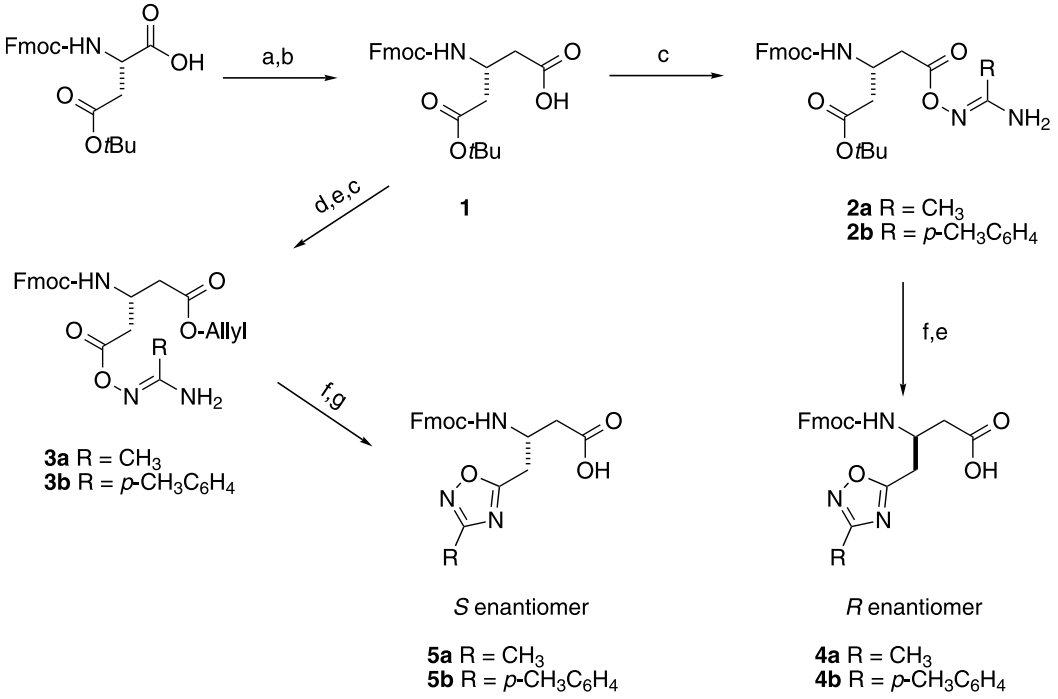
0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01471-0

Arndt–Eistert homologation of Fmoc-L-Asp(O*t*Bu)-OH. We have exploited the symmetry of the resulting β-HomoAsp (β-HAsp) moiety (Fig. 1) to prepare both enantiomers, avoiding the use of the expensive D-Asp derivative.

Synthesis.[26] Both enantiomers of Fmoc-protected 1,2,4-oxadiazole-containing β^3-amino acids were synthesized from Fmoc-(*R*)-β-HAsp(O*t*Bu)-OH **1** (Scheme 1). Compound **1** was obtained by homologation of Fmoc-L-Asp(O*t*Bu)-OH following the Arndt–Eistert procedure. Wolff rearrangement of the intermediate diazoketone was performed using conditions respecting the *N*-Fmoc protection and which were shown to proceed stereospecifically.[24]

The *R* enantiomers of the 1,2,4-oxadiazole derivatives **4a** and **4b** were synthesized in three steps from compound **1** (Fig. 1, R_1 = H, R_2 = *t*-Bu; Scheme 1). The unprotected carboxylic group of **1** was first condensed to various amidoximes which were prepared using classical procedures, i.e. treatment of the corresponding nitrile compounds with hydroxylamine in refluxing ethanol.[27,28] Among the coupling reagents that were tested for the *O*-acylation of amidoximes, DIC/HOBt appeared the most satisfactory while others such as HBTU or EDC/HOBt yielded significant amount of secondary products. It is important to notice that acylation of the β-carboxylic group proceeded without epimerization. The *O*-acyl amidoximes were isolated before being subsequently cyclized. Cyclodehydration to the 1,2,4-oxadiazole ring is generally performed at high temperature (above 100°C) in solvents such as DMF[29,30] or pyridine[31,32] or at room temperature in the presence of a strongly basic reagent (TBAF[33,34]). However, these conditions were not compatible with the base-labile Fmoc protecting group. In the case of DMF and pyridine, this result is probably the consequence of heating together with the presence of nucleophilic amino contaminants in these solvents. Heating in neutral solvents and without dehydrating agent has also been reported for the synthesis of 1,2,4-oxadiazoles.[35,36] However, we found that cyclization proceeded too slowly with the risk of increasing unwanted side reactions. A compromise was found with the use of sodium acetate in refluxing EtOH/H_2O (86°C). These conditions did not induce Fmoc cleavage and cyclization was completed in less than 5 hours in approximately 60% yields.[37] The final removal of the *t*-Bu ester protecting group afforded the chiral Fmoc-(*R*)-β^3-amino acids **4a** and **4b** (Table 1 and Ref. 38).

The corresponding *S* enantiomers **5a** and **5b** were also obtained from compound **1**. Compound **1** was first converted during a protection–deprotection sequence to Fmoc-(*S*)-β-HAsp-OAllyl (90% overall yield).[39] Chiral **5a** and **5b** were then synthesized from Fmoc-(*S*)-β-HAsp-OAllyl (Fig. 1, R_1 = Allyl, R_2 = H, Scheme 1) in three steps as described for **4a** and **4b**, the last step being in this case cleavage of the allyl ester protecting group. It is interesting to note that in addition to Fmoc and *tert*-butyl ester, as well as Boc, Z and benzyl ester (unpublished results), the sodium acetate-catalyzed oxadiazole formation is compatible with the allyl ester



Scheme 1. Synthesis of *S* and *R* enantiomers of Fmoc-protected 1,2,4-oxadiazole-containing β^3-amino acids. *Reagents and conditions:* (a) isobutylchloroformiate, *N*-methyl-morpholine, THF, then diazomethane; (b) silver benzoate (0.1 equiv.), triethylamine (1 equiv.), dioxane, water; (c) amidoxime R-C(=NOH)NH_2, DIC, HOBt, DCM; (d) allyl bromide, Na_2CO_3, DMF; (e) TFA/DCM (50:50); (f) Sodium acetate, EtOH/H_2O, 86°C, 5 h; (g) Pd[PPh_3]$_4$ (0.4 equiv.), morpholine (1.4 equiv.), THF.

Table 1. Physical data of 1,2,4-oxadiazole-containing β^3-amino acids.

Compound	$[\alpha]_D$[a]	Mp (°C)[b]	t_R (min)[c]	Yield (%)
4a	+2[d]	102–104	2.69	48[e]
5a	−2[f]	105–107	2.71	33[g]
4b	−7[d]	135–137	3.41	40[e]
5b	+7[d]	125–127	3.40	43[g]

[a] $t = 20$°C.
[b] Melting points are uncorrected.
[c] Reverse phase HPLC analyses run on a Chromolith SpeedRod C18 column (0.46×5 cm); gradient from A to B in 5 min, 3 mL/min flow rate (A: H_2O, 0.1% TFA; B: CH_3CN, 0.1% TFA); the slight differences in retention times observed between the enantiomers **4a** and **5a**, and **4b** and **5b**, are not significant.
[d] *c* 0.02, DMF.
[e] Overall yield calculated from **1**.
[f] *c* 0.014, DMF.
[g] Overall yield calculated from Fmoc-(*S*)-β-HAsp-OAllyl.

protecting group. Physical data for compounds **5a** and **5b** are presented in Table 1 and Ref. 38.

In conclusion, the use of Fmoc-(*R*)-β-HAsp(O*t*Bu)-OH allowed access to (*R*) and (*S*) enantiomers of the presented Fmoc-protected 1,2,4-oxadiazole-containing β^3-amino acids depending on the carboxylic acid function that is activated. This strategy might be used for the synthesis of various β-HAsp-derived β^3-amino acids. As numerous nitrile-containing compounds are available for the synthesis of amidoximes, a large diversity can be attained for the synthesis of this new series of chiral β^3-amino acids. Finally, sodium acetate is a Fmoc-compatible and efficient catalyst for the formation of the oxadiazole ring.

Acknowledgements

We are grateful to Mr. Pierre Sanchez for his indispensable help in obtaining mass spectrometry data. We thank the Lebanese University for the award of a research fellowship to A.H.

References

1. Crews, P.; Manes, L. V.; Boelher, M. *Tetrahedron Lett.* **1986**, *27*, 2797–2800.
2. De Rosa, S.; De Guilio, A.; Tommonaro, G.; Popov, S.; Kujumgiev, A. *J. Nat. Prod.* **2000**, *63*, 1454–1455.
3. Ojima, I.; Lin, S.; Wang, T. *Curr. Med. Chem.* **1999**, *6*, 927–954.
4. Nicolaou, K. C.; Dai, W. M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15–44.
5. Seebach, D.; Overhand, M.; Kühle, F. N. M.; Martinoni, B. *Helv. Chim. Acta* **1996**, *79*, 913–941.
6. Gademann, K.; Jaun, B.; Seebach, D. *Helv. Chim. Acta* **1999**, *82*, 1–11.
7. Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173–180.
8. DeGrado, W. F.; Schneider, J. P.; Hamuro, Y. *J. Peptide Res.* **1999**, *54*, 206–217.
9. Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219–3232.
10. Seebach, D.; Abele, S.; Schreiber, J. V.; Martinoni, B.; Nussbaum, A. K.; Schild, H.; Schulz, H.; Henneke, H.; Woessner, R.; Bitsch, F. *Chimia* **1998**, *52*, 734–739.
11. Frackenpohl, J.; Arvidsson, P. I.; Schreiber, J. V.; Seebach, D. *Chembiochem* **2001**, *2*, 445–455.
12. Cardillo, G.; Gentilucci, L.; Qasem, A. R.; Sgarzi, F.; Spampinato, S. *J. Med. Chem.* **2002**, *45*, 2571–2578.
13. Sagan, S.; Milcent, T.; Ponsinet, R.; Convert, O.; Tasseau, O.; Chassaing, G.; Lavielle, S.; Lequin, O. *Eur. J. Biochem.* **2003**, *270*, 939–949.
14. Huck, J. PhD Thesis, University of Montpellier II, France, 2002.
15. Behr, L. C. In *The Chemistry of Heterocyclic Compounds*; Weissberger, A., Ed.; John Wiley: New York, 1962; Vol. 17, pp. 245–262.
16. Clapp, L. B. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: New York, 1976; Vol. 20, pp. 65–116.
17. Hemming, K. *J. Chem. Res., Synopses* **2001**, 209–216 and 601–620.
18. Diana, G. D.; Volkots, D. L.; Nitz, J. T.; Bailey, R. T.; Long, M. A.; Vescio, N.; Aldous, S.; Peveur, D. C.; Dutko, F. J. *J. Med. Chem.* **1994**, *37*, 2421–2436.
19. Andersen, K. E.; Jorgensen, A. S.; Braestrup, C. *Eur. J. Med. Chem.* **1994**, *29*, 393–399.
20. Andersen, K. E.; Lundt, B. F.; Joergensen, A. S.; Braestrup, C. *Eur. J. Med. Chem.* **1996**, *31*, 417–425.
21. Naka, T.; Kubo, K. *Curr. Pharm. Des.* **1999**, *5*, 453–472.
22. Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991–8035.
23. Müller, A.; Vogt, C.; Sewald, N. *Synthesis* **1998**, 837–841.
24. Ellmerer, E. P.; Brössner, D.; Maslouh, N.; Tako, A. *Helv. Chim. Acta* **1998**, *81*, 59–65.
25. Ananda, K.; Gopi, H. N.; Suresh Babu, V. V. *J. Peptide Res.* **2000**, *55*, 289–294.
26. Abbreviations of some reagents: DIC, Diisopropylcarbodiimide; EDC, *N*-ethyl-*N*′-(3-dimethylaminopropyl)-carbodiimide hydrochloride; HBTU, 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; HOBt, 1-hydroxybenzotriazole; $Pd[PPh_3]_4$, tetrakis(triphenylphosphine)palladium(0); TBAF, tetra-*n*-butylammonium fluoride; TFA, trifluoroacetic acid.
27. Eloy, F. R. L. *Chem. Rev.* **1962**, *62*, 155–183.
28. Weller, H. N.; Poss, M. A.; E. R. Squibb & Sons, Inc.; US 5,236,916, 17 Aug. 1993.
29. Deegan, T. L.; Nitz, T. J.; Cebzanov, D.; Pufko, D. E.; Porco, J. A., Jr. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 209–212.
30. Poulain, R. F.; Tartar, A. L.; Déprez, B. P. *Tetrahedron Lett.* **2001**, *42*, 1495–1498.
31. Borg, S.; Estenne-Bouhtou, G.; Luthman, K.; Csöregh, I.; Hesselink, W.; Hacksell, U. *J. Org. Chem.* **1995**, *60*, 3112–3120.
32. Buchanan, J. L.; Vu, C. B.; Merry, T. J.; Corpuz, E. G.; Pradeepan, S. G.; Mani, U. N.; Yang, M.; Plake, H. R.; Varkhedkar, V. M.; Lynch, B. A.; MacNeil, I. A.; Loiacono, K. A.; Tiong, C. L.; Holt, D. A. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2359–2364.

33. Rice, K.; Nuss, J. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 753–755.
34. Gangloff, A. R.; Litvak, J.; Shelton, E. J.; Sperandio, D.; Wang, V. R.; Rice, K. D. *Tetrahedron Lett.* **2001**, *42*, 1441–1443.
35. Hébert, N.; Hannah, A. L.; Sutton, S. C. *Tetrahedron Lett.* **1999**, *40*, 8547–8550.
36. Hébert, N.; Hannah, A. L.; Trega Biosciences, WO 00/25768 A1, 11 May 2000.
37. Conversion of the acyl-amidoxime **2b** to the protected oxadiazole derivative. A mixture of compound **2b** (0.33 g, 0.59 mmol) in ethanol (7 mL) and sodium acetate (0.08 g, 0.59 mmol) in water (2 mL) was heated at 86°C for 5 h. The product crystallized upon cooling to room temperature. It was collected by filtration and recrystallized from ethanol to give the protected oxadiazole derivative (1,1-dimethylethyl-3-(*R*)-[[(9*H*-fluoren-9-ylmethoxy)carbonyl]-amino] - 4 - [3 - (4 - methylphenyl) - 1,2,4 - oxadiazol - 5 - yl]-butanoate) as white crystals (0.21 g, 66%): mp 127–129°C; *m*/*z* (ES+) 540.2 (M+H$^+$), 562.2 (M+Na$^+$), 484.3 (M-*t*Bu+H$^+$); HPLC t_R: 4.31 min (see conditions under note *c* of Table 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J=7.1 Hz, 2Ha Fmoc), 7.65 (d, J=7.5 Hz, 2Hd Fmoc), 7.50 (t, J=7.0 Hz, 2He phenyl), 7.30 (t, J=7.5 Hz, 2Hb Fmoc), 7.25–7.18 (m, 4H, 2Hc Fmoc+2Hf phenyl), 5.68 (d, J=8.8 Hz, 1H, NH), 4.52–4.40 (m, 1H, CHα), 4.38–4.22 (m, 2H, CH_2 Fmoc), 4.12 (t, J=6.9 Hz, 1H, CH Fmoc), 3.28 (dd, J=15.6 Hz, 5.8 Hz, 1H, CHβ), 3.18 (dd, J=15.5 Hz, 6.0 Hz, 1H, CHβ), 2.55 (d, J=5.0 Hz, 2H, CH_2β′), 2.38 (s, 3H, CH_3), 1.38 (s, 9H, *t*Bu).
38. Compound **4a**: $C_{22}H_{21}N_3O_5$; 407.15 g/mol; white powder; mp 102–104°C; $[\alpha]_D$=+2 (*c* 0.02, DMF); *m*/*z* (ES+) 408.0 (M+H$^+$), 815.3 (2M+H$^+$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J=7.4 Hz, 2Ha Fmoc), 7.38 (d, J=7.3 Hz, 2Hd Fmoc), 7.20 (t, J=7.3 Hz, 2Hb Fmoc), 7.15 (t, J=7.2 Hz, 2Hc Fmoc), 5.58 (d, J=8.5 Hz, 1H, NH), 4.48–4.32 (m, 1H, CHα), 4.30–4.12 (m, 2H, CH_2 Fmoc), 4.10 (t, J=6.8 Hz, 1H, CH Fmoc), 3.20 (dd, 1H, CHβ), 3.10 (dd, 1H, CHβ), 2.70–2.50 (m, 2H, CH_2β′), 2.2 (s, 3H, CH_3). Compound **4b**: $C_{28}H_{25}N_3O_5$; 483.18 g/mol; white powder; mp 135–137°C; $[\alpha]_D$=−7 (*c* 0.02, DMF); *m*/*z* (ES+) 484.0 (M+H$^+$), 506.4 (M+Na$^+$), 967.5 (2M+H$^+$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J=7.3 Hz, 2Ha Fmoc), 7.70 (d, J=7.5 Hz, 2Hd Fmoc), 7.55 (d, J=6.9 Hz, 2He phenyl), 7.30 (t, J=7.1 Hz, 2Hb Fmoc), 7.32–7.20 (m, 4H, 2Hc Fmoc+2Hf phenyl), 5.80 (d, J=8.6 Hz, 1H, NH), 4.70–4.50 (m, 1H, CHα), 4.42–4.30 (m, 2H, CH_2 Fmoc), 4.20 (t, J=6.4 Hz, 1H, CH Fmoc), 3.40 (dd, J=15.1 Hz, 5.4 Hz, 1H, CHβ), 3.31 (dd, 1H, CHβ), 2.90–2.70 (m, 2H, CH_2β′), 2.40 (s, 3H, CH_3). Compound **5a**: $C_{22}H_{21}N_3O_5$; 407.15 g/mol; R_f 0.67 (0.05% AcOH in EtOAc); mp 105–107°C; $[\alpha]_D$=−2 (*c* 0.014, DMF); *m*/*z* (ES+) 407.8 (M+H$^+$), 815.2 (2M+H$^+$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J=7.5 Hz, 2Ha Fmoc), 7.42 (d, J=7.4 Hz, 2Hd Fmoc), 7.21 (t, J=7.4 Hz, 2Hb Fmoc), 7.16 (t, J=7.4 Hz, 2Hc Fmoc), 5.60 (d, J=8.8 Hz, 1H, NH), 4.48–4.35 (m, 1H, CHα), 4.30–4.18 (m, 2H, CH_2 Fmoc), 4.19 (t, J=6.8 Hz, 1H, CH Fmoc), 3.22 (dd, J=15.6 Hz, 6.3 Hz, 1H, CHβ), 3.12 (dd, J=15.5 Hz, 6.0 Hz, 1H, CHβ), 2.60 (d, J=4.9 Hz, 2H, CH_2β′), 2.28 (s, 3H). Compound **5b**: $C_{28}H_{25}N_3O_5$; 483.18 g/mol; R_f 0.7 (1% AcOH in EtOAc); mp 125–127°C; $[\alpha]_D$=+7 (*c* 0.02, DMF); *m*/*z* (ES+) 484.3 (M+H$^+$), 967.2 (2M+H$^+$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J=8.1 Hz, 2Ha Fmoc), 7.55 (d, J=7.3 Hz, 2Hd Fmoc), 7.38 (d, J=7.6 Hz, 2He phenyl), 7.20 (t, J=7.4 Hz, 2Hb Fmoc), 7.20–7.10 (m, 4H, 2Hc Fmoc+2Hf phenyl), 5.58 (d, J=8.0 Hz, 1H, NH), 4.50–4.32 (m, 1H, CHα), 4.30–4.12 (m, 2H, CH_2 Fmoc), 4.05 (t, J=7.0 Hz, 1H, CH Fmoc), 3.35–3.10 (m, 2H, CH_2β), 2.90–2.60 (m, 2H, CH_2β′), 2.28 (s, 3H, CH_3).
39. Synthesis of Fmoc-(S)-β-HAsp-OAllyl. A mixture of Fmoc-(R)-β-HAsp(O*t*Bu)-OH **1** (0.5 g, 1.18 mmol), sodium carbonate (0.25 g, 2.36 mmol) and allylbromide (0.18 mL, 2.12 mmol) in DMF (10 mL) was stirred at room temperature for 18 h. After this period, the solvent was removed under reduced pressure and the residue was dissolved in EtOAc. The organic layer was washed with 10% aqueous $NaHCO_3$, 1 M $KHSO_4$, brine, and dried over $MgSO_4$. Evaporating the solvent under vacuum afforded crude Fmoc-(R)-β-HAsp(O*t*Bu)-OAllyl which was purified by flash chromatography on a silica gel column (EtOAc/hex, 3:7). Colorless oil (0.523 g, 95%): R_f 0.54 (EtOAc/hex, 3:7); *m*/*z* (ES+) 466.1 (M+H$^+$), 487.7 (M+Na$^+$), 410.2 (M-*t*Bu+H$^+$), 931.2 (2M+H$^+$); HPLC t_R: 3.79 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J=7.5 Hz, 2Ha Fmoc), 7.60 (d, J=7.3 Hz, 2Hd Fmoc) 7.40 (t, J=7.4 Hz, 2Hb Fmoc), 7.31 (t, J=7.3 Hz, 2Hc Fmoc), 6.00–5.85 (m, 1H, CH allyl), 5.50 (d, J=8.8 Hz, 1H, NH), 5.30 (q, J=10.2 Hz, 1.4 Hz, 2H, C=CH_2 allyl), 4.60 (d, J=5.7 Hz, 2H, O-CH_2 allyl), 4.38 (d, J=7.1 Hz, 2H, CH_2 Fmoc), 4.23 (t, J=6.9 Hz, 1H, CH Fmoc), 2.80 (dd, J=16.6 Hz, 5.7 Hz, 1H, CHβ), 2.68 (dd, J=6.1 Hz, 1H, CHβ), 2.60 (t, J=6.8 Hz, 2H, CH_2β′), 1.42 (s, 9H, *t*Bu). The preceding *tert*-butyl-protected compound (0.517 g, 1.11 mmol) was treated with a 50% TFA solution in DCM (8 mL) for 2 h at room temperature. The solvents were then removed under reduced pressure and a mixture of hexane/diethyl ether was added to the residue. The compound Fmoc-(S)-β-HAsp-OAllyl precipitated as a white powder and was collected by filtration (0.425 g, 94%): $C_{23}H_{23}NO_6$; 409.15 g/mol; mp 84–86°C; *m*/*z* (ES+) 409.9 (M+H$^+$), 432.2 (M+Na$^+$), 819.0 (2M+H$^+$); HPLC t_R: 2.99 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J=7.5 Hz, 2Ha Fmoc), 7.50 (d, J=7.4 Hz, 2Hd Fmoc), 7.31 (t, J=7.4 Hz, 2Hb Fmoc), 7.22 (t, J=6.8 Hz, 2Hc Fmoc), 5.90–5.76 (m, 1H, CH allyl) 5.55 (d, J=8.3 Hz, 1H, NH), 5.22 (q, J=9.5 Hz, 1.4 Hz, 2H, C=CH_2 allyl), 4.50 (d, J=5.4 Hz, 2H, O-CH_2 allyl), 4.38–4.28 (m, 2H, CH_2 Fmoc), 4.18 (t, J=6.7 Hz, 1H, CH Fmoc), 2.80–2.58 (m, 4H, CH_2β+CH_2β′).