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# Facile synthesis of 2-(β-*C*-glucopyranosyl)-β-amino acid: a new class of glycopeptide building block

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**Abstract**—A convenient preparation of both stereoisomers of a (2*R*)/(2*S*)-2-*C*-glycosylated β-amino acid is described. β-*C*-Glycoside was formed by the reaction of α-acetobromoglucose with carbanion of cyanoacetate. The steric bulk of the *C*-glycoside moiety does not hinder amino acid coupling, showing the utility of this carbohydrate-containing building block for glycopeptide synthesis.

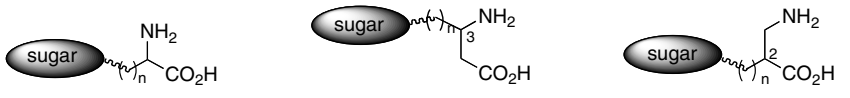

## 1. Introduction

As promising building blocks for the artificial glycopeptides, *C*-glycosyl amino acids are of particular interest due to their stability toward chemical and enzymatic degradation.[1] α-*C*-Glycosylglycine and its methylene chain tethered derivatives (Chart 1, **I**) have been synthesized from glycosyl halides,[2–7] glycals,[8–10] allyl-*C*-glycosides,[11,12] sugar nitrones,[13] and sugar δ-lactones.[14,15] While the methodology of the C–C bond formation reactions and stereochemistry of the observed products with respect to the configuration of the anomeric center and/or the α-carbon of the amino acid moiety have been extensively studied for these synthetic *C*-glycosyl amino acids, only a small number of them have been utilized for *C*-glycosylpeptide synthesis.[16–20]

β-Peptides have been shown to adopt helixes, sheets, and turns, which are the main structural elements of natural α-peptides.[21] In addition, β-peptides are also known to have greater resistance toward enzymatic degradation.[22] While several examples demonstrating the preparation of *C*-glycosyl-β$^3$-amino acid derivatives (**II**)[23–27] and helical diversity and robustness of β-glycopeptides derived from them[28–30] have been reported, there has been only one example that describes the preparation of *C*-glycosyl-β$^2$-amino acid derivatives (**III**), in which *furanose* moiety was employed as a sugar part.[31] To the best of our knowledge, the synthesis of *C*-glycosyl-β$^2$-amino acid derivative (**III**) with *pyranose* sugar has never been reported to date in spite of its simple and important structure. In this letter, a practical preparation for both stereoisomers of (2*R*)/(2*S*)-2-β-*C*-glucopyranosyl β-amino acid (**III**, $n = 0$) and their applicability toward peptide synthesis are described.

## 2. Results and discussion

In contrast to the wide availability of β$^3$-amino acids, a versatile synthetic strategy for β$^2$-amino acids is lacking.[32,33] The key reaction in the present study is the




*C*-glycosyl α-amino acid **I** | *C*-glycosyl β$^3$-amino acid **II** | *C*-glycosyl β$^2$-amino acid **III**

**Chart 1.**

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stereocontrolled *C*-glycoside formation achieved by an $S_N2$ reaction of α-acetobromoglucose (**1**) with the carbanion of cyanoacetate ester, affording the β-peptide backbone upon reduction.[34] Similar procedure has been employed for synthesis of *C*-glycosyl 1,3-propanediamines using malononitrile as a carbanion source.[35] The β-anomers **2** and **3** were obtained exclusively with complete inversion at the anomeric carbon. The diastereomers (**2**/**3** = 25/75) with respect to the asymmetric center at the C2 atom of the side chain interconvert easily because of the acidic nature of the C2-hydrogen in **2** and **3**. The configuration assignment of **3** (β-anomer, 2S) is secured by X-ray analysis (data not shown). Subsequent hydrogenation of the nitrile moiety of **2**/**3** by $PtO_2$ in EtOH/$CHCl_3$ affords diastereomeric mixture of **4** and **5** (62:38). The mixture of amine hydrochlorides **4**/**5** can be separated by recrystallization from methanol-ether to afford a single diastereomer **5**. The absolute configuration of amine hydrochloride **5** was determined to be 2*S* by X-ray crystallography (Fig. 1).[36] The amine hydrochlorides **4**/**5** were converted to Fmoc derivatives **6**/**7** by Fmoc–*N*-hydroxysuccinimide ester and triethylamine in MeOH/$CH_3CN$. No epimerization of the compounds **4**/**5** and **6**/**7** was observed during the transformations to the Fmoc derivative.

Thus, the facile preparation of Fmoc–amino acids **8** and **9** is summarized in Scheme 1.[37] Compounds **2**/**3** and **4**/**5** were used as diastereomeric mixtures and the isomers were separated by column chromatography after Fmoc protection, affording **6** and **7** in 25% and 10% overall yield, respectively (based on **1**). Deprotection of *t*-butyl group was conducted by formic acid in essentially quantitative yield. Figure 2 shows the crystal structure of compound **9**, confirming the assignment of the absolute configuration of the compounds.[36]

The feasibility of coupling of the *C*-glycosylamino acids with L-phenylalanine was examined to ascertain whether the steric bulk of the appended carbohydrate would hinder the reaction. To demonstrate the reactivity of both amine and carboxylate moiety in the present glucopyranosylamino acid, we examined the reaction of amines **4**/**5** and carboxylates **8**/**9** with L-phenylalanine counterparts **13** and **10**, respectively.

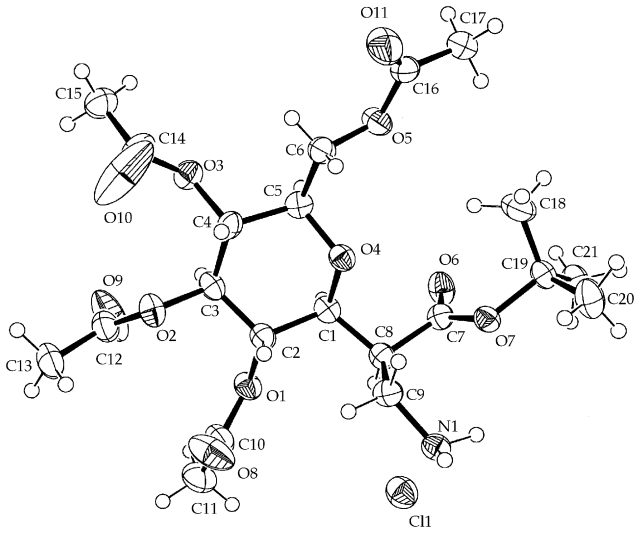



**Figure 1.** ORTEP plot for **5**.

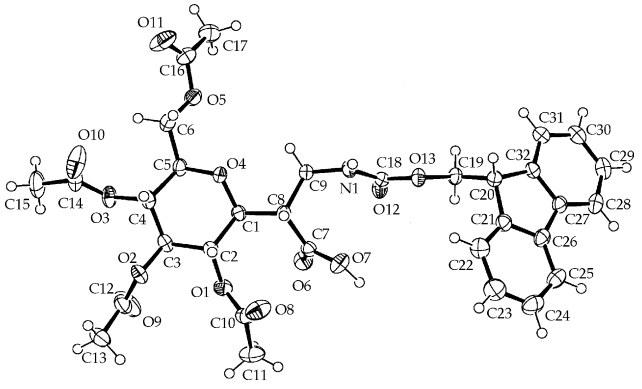
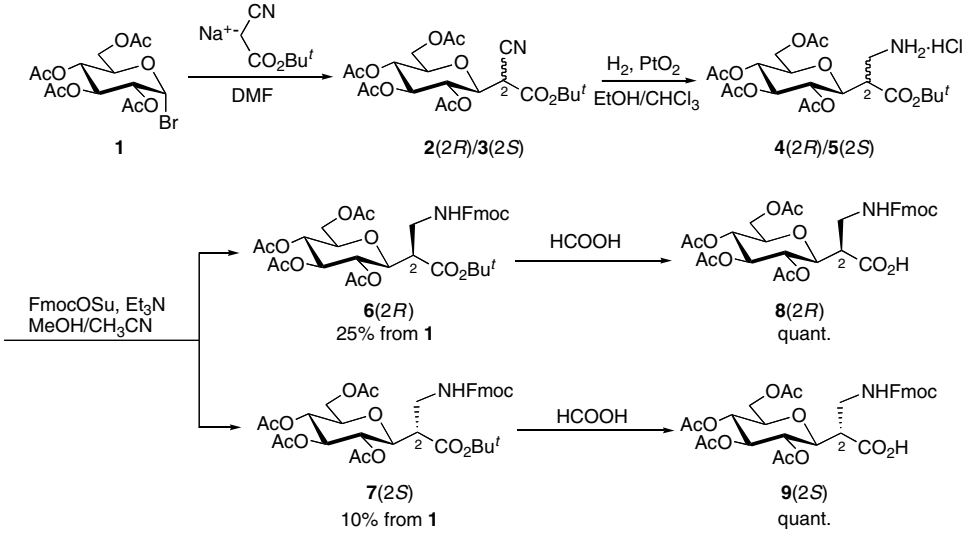
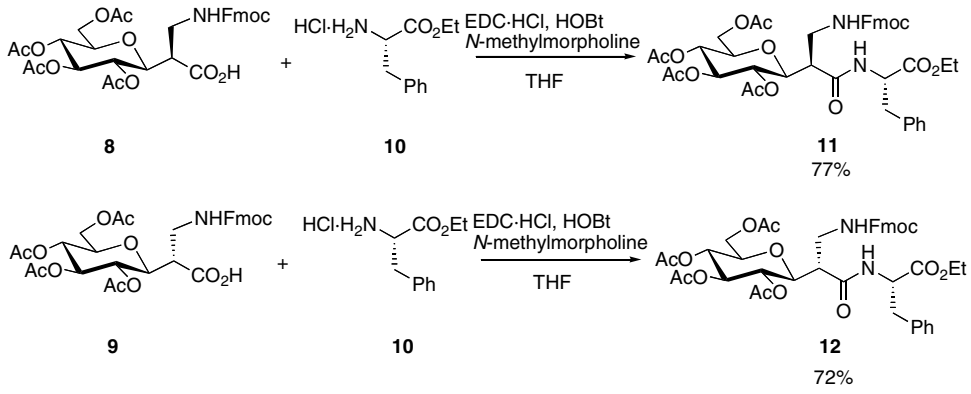


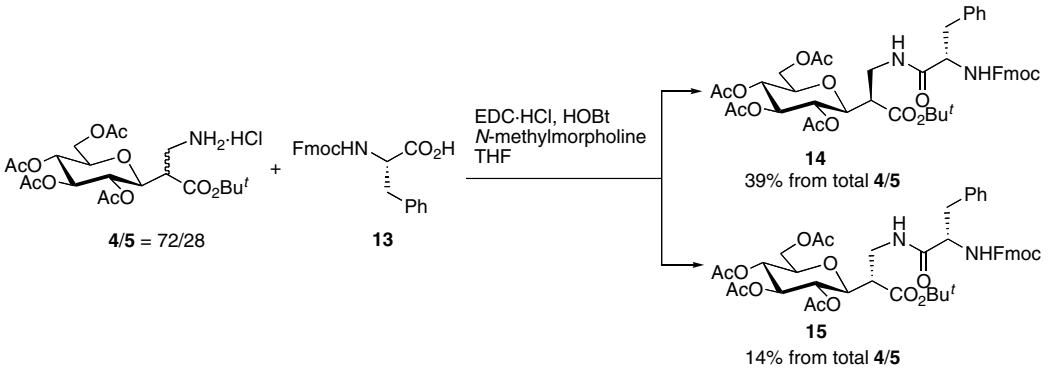

**Figure 2.** ORTEP plot for **9**.




**Scheme 1.** Synthesis of **8** and **9**.




**Scheme 2.** Coupling reaction for carboxylate group.




**Scheme 3.** Coupling reaction for amino group.

Initially, diasteromerically-pure **8** and **9** were reacted with L-phenylalanine ethyl ester hydrochloride **10** in the presence of EDC·HCl, HOBt, and *N*-methylmorpholine (Scheme 2). Reaction of both stereoisomers afforded dipeptides **11** and **12** in good yields.[38]

Subsequently, amines **4/5** were coupled with Fmoc–L-phenylalanine **13** under the same conditions. Due to the difficulty in obtaining diastereomerically-pure **4**, amine compound **4/5** was used as a diastereomeric mixture (**4/5** = 72/28). The obtained products were purified by silica gel column chromatography to afford the resolved dipeptides **14** and **15** in 39% and 14% yields respectively, in which the absolute configuration of the stereocenter of the compounds was determined based on the product yield[39] (Scheme 3).

In summary, we have developed the synthesis of Fmoc-protected 2-(β-*C*-glucopyranosyl)-β-amino acid derivatives **8** and **9** as a novel class of *C*-glycosyl amino acids by a convenient procedure. To the best of our knowledge, this is the first example for the synthesis of *C*-glycopyranosyl-$\beta^2$-amino acid derivative. Readily available, well-resolved diastereomers with respect to the α-carbon (C2) should provide versatile carbohydrate-containing β-amino acid building blocks for glycopeptide research. As a peptide building block, the sugar moiety does not prevent amino acid coupling for both stereoisomers of **4/5** and **8/9**. The present method should allow the application to the other carbohydrates and to the preparation of longer *C*-glycopeptides.

## Acknowledgements

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37. *Selected data for* **8**: $^1$H NMR ($CD_3OD$) $\delta$ (ppm): 7.83 (2H, d, $J = 7.3$ Hz, Fmoc-Ar), 7.68 (2H, d, $J = 7.3$ Hz, Fmoc-Ar), 7.43 (2H, dd, $J = 7.3$, 6.7 Hz, Fmoc-Ar), 7.36 (2H, dd, $J = 7.3$, 6.7 Hz, Fmoc-Ar), 7.09 (1H, br, NHCOO), 5.34 (1H, dd, $J = 9.3$, 9.8 Hz, H-2), 5.22 (1H, dd, $J = 9.3$, 9.6 Hz, H-3), 5.05 (1H, dd, $J = 9.6$, 9.8 Hz, H-4), 4.42 (2H, m, Fmoc–$CH_2$O), 4.26–4.10 (3H, m, H-6, Fmoc–CH), 3.86 (1H, dd, $J = 2.4$, 9.8 Hz, H-1), 3.75 (1H, m, H-5), 3.73 (2H, m, H-β), 2.92 (1H, m, H-α), 2.06 (3H, s, Ac, $COCH_3$), 2.05 (3H, s, Ac, $COCH_3$), 2.00 (3H, s, Ac, $COCH_3$), 1.99 (3H, s, Ac, $COCH_3$). $^{13}$C NMR ($CD_3OD$) $\delta$ (ppm): 173.13, 172.37, 171.85, 171.22, 171.06 (Ac, O*C*O, *C*OOH), 158.64 (NH*C*OO), 145.27, 145.17, 142.55 (Fmoc-Ar, C), 128.80, 128.17, 126.10, 120.94 (Fmoc-Ar, CH), 76.98 (C-5, C-1), 76.20 (C-3), 70.99 (C-2), 69.53 (C-4), 67.56 (Fmoc–*C*$H_2$O), 63.22 (C-6), 48.43 (Fmoc–*C*H), 46.28 (C-α), 39.79 (C-β), 20.65, 20.62, 20.52 (Ac, CO*C*$H_3$). ESI-MS Calcd for $C_{32}H_{35}NO_{13}Na$ $(M+Na)^+$: 664.20. Found: 664.23. Anal. Calcd for $C_{33}H_{39}O_{14}N$ (**8**·$CH_3OH$): C, 58.84; H, 5.84; N, 2.08. Found: C, 59.31; H, 5.55; N, 2.22. For **9**: mp 95–96 °C. $^1$H NMR ($CD_3OD$) $\delta$ (ppm): 7.83 (2H, d, $J = 7.5$ Hz, Fmoc-Ar), 7.69 (2H, d, $J = 7.3$ Hz, Fmoc-Ar), 7.43 (2H, dd, $J = 7.5$ Hz, Fmoc-Ar), 7.35 (2H, dd, $J = 7.3$, 7.5 Hz, Fmoc-Ar), 5.25 (1H, dd, $J = 9.5$, 9.2 Hz, H-3), 5.12 (1H, dd, $J = 9.8$, 9.5 Hz, H-2), 5.07 (1H, dd, $J = 9.2$, H-4), 4.36–4.26 (4H, m, $J = 6.41$, 5.19 Hz, Fmoc–$CH_2$O, Fmoc–C*H*, H-6a), 4.14–4.06 (2H, m, H-6b, H-1), 3.82 (1H, m, H-5), 3.54 (2H, m, H-β), 2.83 (1H, m, H-α), 2.06 (6H, s, Ac, $COCH_3$), 2.03 (3H, s, Ac, $COCH_3$), 1.99 (3H, s, Ac, $COCH_3$). $^{13}$C NMR($CD_3OD$) $\delta$ (ppm): 174.54, 172.34, 171.76, 171.24, 171.21 (Ac, O*C*O, *C*OOH), 158.51 (NH*C*OO), 145.34, 145.25, 142.50 (Fmoc-Ar, C), 128.75, 128.14, 126.24, 120.90 (Fmoc-Ar, CH), 77.87 (C-1), 75.83 (C-5), 75.83 (C-3), 71.94 (C-2), 69.76 (C-4), 67.80 (Fmoc–*C*$H_2$O), 63.34 (C-6), 48.37 (Fmoc–*C*H), 47.88 (C-α), 39.50 (C-β), 20.64 (Ac, CO*C*$H_3$). ESI-MS Calcd for $C_{32}H_{35}NO_{13}Na$ $(M+Na)^+$: 664.20. Found: 664.22. Anal. Calcd for $C_{33}H_{39}O_{14}N$ (**9**·$CH_3OH$): C, 58.84; H, 5.84; N, 2.08. Found: C, 59.12; H, 5.58; N, 2.21.
38. *Selected data for* **11**: $^1$H NMR ($CDCl_3$, $Me_4Si$) $\delta$ (ppm): 7.77 (2H, d, $J = 7.3$ Hz, Fmoc-Ar), 7.58 (2H, d, $J = 7.3$ Hz, Fmoc-Ar), 7.41 (2H, dd, $J = 7.3$, 7.6 Hz, Fmoc-Ar), 7.35–7.21 (7H, m, Fmoc-Ar, Phe-Ar), 7.14 (1H, d, $J = 8.2$ Hz, peptide–N*H*CO), 5.15 (1H, dd, $J = 9.2$, 9.5 Hz, H-3), 5.04–4.90 (4H, m, H-2, H-4, Phe–C*H*, N*H*COO), 4.34 (2H, $J = 7.3$ Hz, Fmoc–$CH_2$O), 4.25 (2H, q, $J = 7.0$ Hz, Et ester–$CH_2CH_3$), 4.23 (2H, m, Fmoc–C*H*, H-6a), 4.02 (1H, d, $J = 10.7$ Hz, H-6b), 3.72–3.45 (3H, m, H-5, H-1, H-β), 3.36–3.24 (2H, m, H-β, Phe–$CH_2$), 3.06 (1H, dd, $J = 8.2$, 14.0 Hz, Phe–$CH_2$), 2.57 (1H, m, H-α), 2.05 (3H, s, Ac, $COCH_3$), 2.03 (3H, s, Ac, $COCH_3$), 2.01 (3H, s, Ac, $COCH_3$), 1.99 (3H, s, Ac, $COCH_3$), 1.31 (3H, t, $J = 7.0$ Hz, Et ester–$CH_2CH_3$). $^{13}$C NMR ($CDCl_3$, $Me_4Si$) $\delta$ (ppm): 171.30, 170.65, 170.10, 169.32, 168.69 (Ac, O*C*O, peptide–NH*C*O), 156.41 (NH*C*OO), 143.86, 143.73, 141.23 (Fmoc-Ar, C), 136.43 (Phe-Ar, C), 129.13, 128.55 (Phe-Ar, CH), 127.64, 127.13, 127.00, 125.04, 124.97, 119.93 (Fmoc-Ar, CH), 76.24 (C-5, C-1), 73.99 (C-3), 69.87 (C-2), 67.99 (C-4), 66.58 (Fmoc–*C*$H_2$O), 61.76 (C-6), 61.63 (Et ester–*C*$H_2CH_3$), 53.35, 53.17 (Phe–*C*H), 47.10 (Fmoc–*C*H), 46.83 (C-α), 41.18 (C-β), 37.57 (Phe–*C*$H_2$), 20.68, 20.57, 20.48 (Ac, CO*C*$H_3$), 14.11, 14.03 (Et ester–$CH_2CH_3$). ESI-MS Calcd for $C_{43}H_{48}N_2O_{14}Na$ $(M+Na)^+$: 839.30. Found: 839.27. Anal. Calcd for $C_{43}H_{50}N_2O_{15}$ (**11**·$H_2O$): C, 61.86; H, 6.04; N, 3.36. Found: C, 61.59; H, 5.96; N, 3.27. For **12**: mp 184–185 °C. $^1$H NMR ($CDCl_3$, $Me_4Si$) $\delta$ (ppm): 7.76 (2H, d,

$J = 7.3$ Hz, Fmoc-Ar), 7.61 (2H, d, $J = 7.3$ Hz, Fmoc-Ar), 7.40 (2H, dd, $J = 7.3$ Hz, Fmoc-Ar), 7.33–7.20 (5H, m, Fmoc-Ar, Phe-Ar), 7.13 (2H, $J = 7.0$ Hz, Phe-Ar), 6.80 (1H, d, $J = 7.9$ Hz, peptide–N*H*CO), 5.38 (1H, dd, N*H*COO), 5.14 (1H, dd, $J = 9.16$ Hz, H-3), 5.03 (2H, dd, $J = 9.8$, 9.5 Hz, H-2, H-4), 4.86 (1H, dd, $J = 6.7$, 7.0 Hz, Phe–CH), 4.37 (2H, m, Fmoc–$CH_2$O), 4.19 (3H, t, $J = 7.0$, 7.3 Hz, Fmoc–C*H*, Et ester–$CH_2CH_3$), 4.09 (1H, dd, $J = 4.3$, 12.5 Hz, H-6a), 4.02 (1H, dd, $J = 11.6$ Hz, H-6b), 3.85 (1H, m, H-5), 3.52–3.40 (3H, m, H-β, H-1), 3.19 (1H, $J = 5.8$, 14.0 Hz, Phe–$CH_2$), 3.05 (1H, $J = 7.0$, 14.0 Hz, Phe–$CH_2$), 2.62 (1H, m, H-α), 2.03 (6H, s, Ac, $COCH_3$), 2.00 (3H, s, Ac, $COCH_3$), 1.98 (3H, s, Ac, $COCH_3$), 1.25 (3H, t, Et ester, $CH_2CH_3$). $^{13}$C NMR ($CDCl_3$, $Me_4Si$) $\delta$ (ppm): 171.26, 17.67, 170.16, 169.92, 169.37 (Ac, O*C*O, peptide–NH*C*O), 156.43 (NH*C*OO), 143.86, 141.22 (Fmoc-Ar, C), 135.96 (Phe-Ar, C), 129.16, 128.45 (Phe-Ar, CH), 127.64, 127.00, 125.10, 119.91 (Fmoc-Ar, CH), 76.43 (C-5), 76.14 (C-1), 74.06 (C-3), 69.65 (C-2), 67.94 (C-4), 66.79 (Fmoc–*C*$H_2$O), 61.60 (C-6, Et ester–*C*$H_2CH_3$), 53.02 (Phe–*C*H), 48.05 (C-α), 47.12 (Fmoc–CH), 38.95 (C-β), 37.72 (Phe–*C*$H_2$), 20.57, 20.47 (Ac, CO*C*$H_3$), 14.06, 14.00 (Et ester–$CH_2CH_3$). ESI-MS Calcd for $C_{43}H_{48}N_2O_{14}Na$ $(M+Na)^+$: 839.30. Found: 839.32. Anal. Calcd for $C_{43}H_{48}N_2O_{14}$ (**12**): C, 63.23; H, 5.92; N, 3.43. Found: C, 62.94; H, 5.93; N, 3.45.

39. *Selected data for* **14**: $^1$H NMR ($CDCl_3$, $Me_4Si$) $\delta$ (ppm): 7.76 (2H, d, $J = 7.6$ Hz, Fmoc-Ar), 7.53 (2H, dd, $J = 6.7$, 7.0 Hz, Fmoc-Ar), 7.40 (2H, dd, $J = 6.0$, 7.6 Hz, Fmoc-Ar), 7.35–7.19 (7H, m, Fmoc-Ar, Phe-Ar), 6.28 (1H, br, peptide–N*H*CO), 5.37 (1H, br, N*H*COO), 5.30 (1H, dd, $J = 8.9$, 10.1 Hz, H-2), 5.10 (1H, dd, $J = 8.9$, 9.5 Hz, H-3), 5.03 (1H, dd, $J = 9.5$ Hz, H-4), 4.45–4.33 (3H, m, Fmoc–$CH_2$O, Phe–CH), 4.20–4.05 (3H, m, H-6, Fmoc–CH), 3.62 (1H, m, H-β), 3.54–3.46 (2H, m, H-5, H-1), 3.35 (1H, m, H-β′), 3.07 (2H, br, Phe–$CH_2$), 2.70 (1H, t, $J = 5.65$ Hz, H-α), 2.03 (6H, s, Ac, $COCH_3$), 2.02 (3H, s, Ac, $COCH_3$), 2.00 (3H, s, Ac, $COCH_3$), 1.43 (9H, s, *t*-Bu, $(CH_3)_3C$). $^{13}$C NMR ($CDCl_3$, $Me_4Si$) $\delta$ (ppm): 170.83, 170.63, 170.37, 169.26, 169.19, 168.90 (Ac, O*C*O, *C*OO, peptide–NH*C*O), 155.72 (NH*C*OO), 143.68, 143.65, 141.23 (Fmoc-Ar, C), 136.33 (Phe-Ar, C), 129.23, 128.76 (Phe-Ar, CH), 127.69, 127.14, 127.03, 124.97, 119.96 (Fmoc-Ar, CH), 82.31 (*t*-Bu, $(CH_3)_3C$), 76.77 (C-1), 75.95, 75.82 (C-5), 74.59 (C-3), 69.59 (C-2), 67.96 (C-4), 67.00 (Fmoc–*C*$H_2$O), 61.74 (C-6), 56.29 (Phe–*C*H), 47.04 (Fmoc–*C*H), 45.32 (C-α), 38.65 (C-β, Phe–*C*$H_2$), 28.02, 27.93 (*t*-Bu, (*C*$H_3$)$_3$C), 20.63, 20.58 (Ac, CO*C*$H_3$). ESI-MS Calcd for $C_{45}H_{52}N_2O_{14}Na$ $(M+Na)^+$: 867.33. Found: 867.25. For **15**: mp 79–82 °C. $^1$H NMR ($CDCl_3$, $Me_4Si$) $\delta$ (ppm): 7.76 (2H, d, $J = 7.5$ Hz, Fmoc-Ar), 7.53 (2H, dd, $J = 7.3$, 7.9 Hz, Fmoc-Ar), 7.40 (2H, dd, $J = 7.3$, 7.5 Hz, Fmoc-Ar), 7.33–7.18 (7H, m, Fmoc-Ar, Phe-Ar), 6.43 (1H, br, peptide–N*H*CO), 5.47 (1H, br, N*H*COO), 5.18 (1H, dd, $J = 8.5$, 9.5 Hz, H-3), 5.07 (1H, dd, $J = 7.3$, 9.6 Hz, H-2), 5.01 (1H, dd, $J = 8.5$, 9.5 Hz, H-4), 4.40 (2H, m, Fmoc–$CH_2$O, Phe–CH), 4.25–4.15 (3H, m, Fmoc–$CH_2$, Fmoc–C*H*, H-6a), 4.06–4.01 (2H, m, H-6b, H-1), 3.73–3.58 (2H, m, H-β, H-5), 3.38 (1H, m, H-β′), 3.10–2.95 (2H, m, Phe–$CH_2$), 2.53 (1H, m, H-α), 2.06 (3H, s, Ac, $COCH_3$), 2.02 (6H, s, Ac, $COCH_3$), 2.00 (3H, s, Ac, $COCH_3$), 1.43 (9H, s, *t*-Bu, $(CH_3)_3C$). $^{13}$C NMR ($CDCl_3$, $Me_4Si$) $\delta$ (ppm): 170.75, 170.58, 170.39, 170.12, 169.44, 169.31 (Ac, O*C*O, *C*OO, peptide–NH*C*O), 155.78 (NH*C*OO), 143.74, 143.74, 141.22 (Fmoc-Ar, C), 136.53 (Phe-Ar, C), 129.23, 128.53 (Phe-Ar, CH), 127.64, 127.00, 125.12, 125.04, 119.91 (Fmoc-Ar, CH), 81.94 (*t*-Bu,$(CH_3)_3C$), 77.24 (C-1), 77.18 (C-5), 74.49 (C-3), 69.04 (C-2), 68.44 (C-4), 66.97 (Fmoc–*C*$H_2$O), 62.20 (C-6), 56.11 (Phe–*C*H), 47.05 (Fmoc–*C*H), 45.60 (C-α), 38.69 (C-β), 35.47 (Phe–*C*$H_2$), 28.02, 27.91 (*t*-Bu, (*C*$H_3$)$_3$C), 20.73, 20.58, 20.52 (Ac, CO*C*$H_3$). ESI-MS Calcd for $C_{45}H_{52}N_2O_{14}Na$ $(M+Na)^+$: 867.33. Found: 867.35. Anal. Calcd for $C_{46}H_{54}N_2O_{14}$ (**15**·$H_2O$): C, 62.63; H, 6.31; N, 3.25. Found: C, 62.79; H, 6.26; N, 3.24.