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Synthesis of new *C*-glycosyl aza-β^3-amino acids building blocks

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ABSTRACT

New C-glycosylated N^{β}-protected aza-β^3-amino acid building blocks have been prepared from *C*-glycosyl aldehydes of *gluco* and *galacto* configuration by reductive amination and subsequent N-alkylation. These moieties were elaborated to β-dipeptides by elongation at the C- or the N-terminus establishing their ability to be incorporated in original glycosylated foldamers.

Organized molecular structures have always fascinated chemists and the construction of representatives of this class of compounds is still a challenge. Nature offers a number of models of highly organized molecules among which the helix occupies a prominent place. This tridimensional folding pattern found in nucleic acids and in proteins plays an important role in molecular recognition and in cellular communication. The construction of artificial oligomers able to adopt such an organized shape without external help has long been a holy grail. The discovery by Gellman[1] and Seebach[2] that analogs of amino acids can be assembled into oligomers, the so-called foldamers,[3] showing a strong tendency to spontaneously arrange in ordered tridimensional structures such as helices[4] has prompted many groups to design such oligomers and to examine their spatial arrangements. In this regard, β-peptides have been the subject of intense interest, and their oligomers or mixed oligomers are able to adopt diverse helical structures. It has been shown that stable 14-, 12-, and mixed 10/12-helices are formed in short oligomers of acyclic- or cyclic β-amino acids.[5] Various β-amino acid monomers have been used including β-amino-acids derived from sugars as building blocks.[6] In-depth studies by Sharma et al. showed that 5-amino furanose derived amino acid oligomers also adopt helical structures.[7] We have shown for example that small oligomers (6 to 8-mers) of conformationally restricted anomeric β-amino acids[8] can adopt organized structures.[9] As glycosylation is an important post-translational process which seems to play a role in protein structuration, it would be of interest to examine the behavior of oligopeptides bearing a glucidic part not necessarily embedded in the peptidic backbone. Organized structures built with such glycosylated units would be of interest as glycopeptides mimics[10] or as multivalent carbohydrate presenting structure.

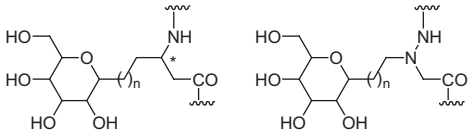

Figure 1. Sugar amino acid building blocks.

Thus we decided to investigate the creation of new building blocks incorporating a glucidic part—a glucose or galactose unit linked to a β-amino-acid by a stable C-glycosidic linkage. Ample precedents from literature show that a spacer arm of two methylene groups should be suitable.[11] (Fig. 1) This sugar β-amino-acid should retain the properties of a carbohydrate, for example in recognition process and the properties of the β-amino-acid when incorporated into an oligomer. If the synthesis of C-glycosidic α-amino acids has been thoroughly investigated,[11] the synthesis of *C*-glycosyl β^3-amino-acids (Compound **I** Fig. 1) remains scarcely explored,[6d] and is still challenging mainly due to the difficulty to create stereoselectively a stereocenter remote from the chiral sugar template.

The use of aza-β^3-amino acids[12] as a surrogate of amino acids in the construction of peptidomimetics[13] and foldamers[14] proved

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useful. Thus we devised glycosylated aza-β^3-amino acids (Compound **II** Fig. 1). We describe in this Letter the synthesis of these chiral building blocks and selected dipeptides resulting from their coupling with β-alanine.

Two biologically significant model sugars were chosen as glycosidic moieties. The first, of β anomeric configuration was derived from glucose while the second, of α anomeric configuration was derived from galactose. This gave us the opportunity to examine the influence of the anomeric configuration and two different types of sugar protecting groups.

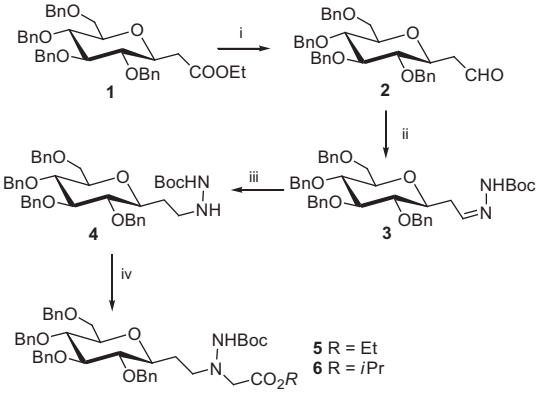
The known β-*C*-glucosyl derivative **1** was prepared as a single anomer from commercially available 2,3,4,6-tetra-*O*-benzylglucopyranose by a Wittig-type reaction.[15] The reduction of the ethyl ester by reaction with DIBAL-H in toluene led to corresponding aldehyde **2** (Scheme 1). On treatment of **2** with *N*-*tert*-butyloxycarbonylhydrazine in refluxing toluene, the hydrazone **3** was formed in 90% yield as a single isomer.[16] The reduction of the *C*–*N* double bond with sodium cyanoborohydride afforded the hydrazine derivative **4** in excellent yield.[17] The N^2 alkylation of **4** with ethyl and isopropylbromoacetates was carried out in toluene in the presence of K_2CO_3 leading to 1-*tert*-butoxycarbonyl-2-carboxy alkyloxyhydrazine derivatives **5–6** in 82 and 70% yields respectively.[18] The deprotection of *N*^{1}-*tert*-butyloxycarbonyl group of the ethyl derivative **5** proved difficult giving a modest yield of the pure compound. The glycosylated aza-β-aminoester **6** gave better results and was selected as the chiral building block for further peptidic coupling.

The ability of compound **6** to be incorporated in a β-peptidic chain was then tested by chain elongation either at the C- or at the N-terminus (Scheme 2). First, compound **6** was converted into the corresponding hydrazinium salt **7** on exposure to TFA in CH_2Cl_2 at 0 °C (84% yield). The coupling between **7** and the *N*-Boc-β-alanine in the presence of isobutylchloroformate and *N*-methyl morpholine at room temperature led to the desired aza-β-dipeptide **8** in 60% yield.[19]

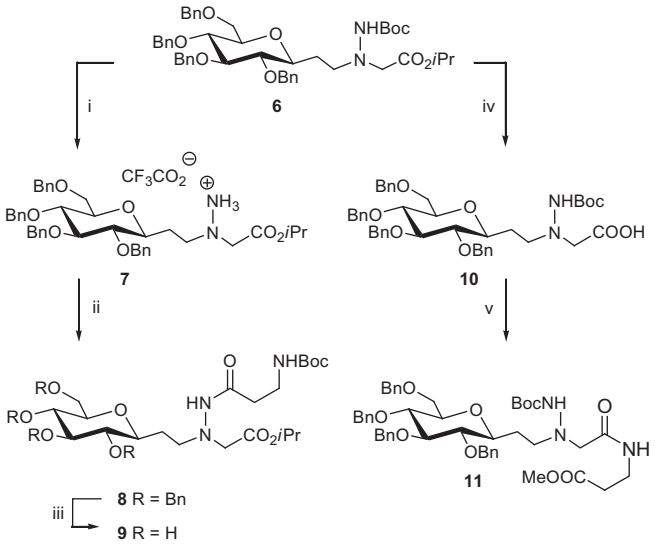
The removal of the sugar benzyl groups was tested on compound **8**. Catalytic hydrogenation under hydrogen pressure in the presence of $Pd(OH)_2$/C in a mixture of CH_2Cl_2/MeOH gave the free derivative **9** in 90% yield.

For C-terminus expansion, the removal of the isopropyl group of **6** was carried out by treatment with potassium hydroxide in MeOH. The resulting free acid **10** was coupled with H-β-alanine-OMe under the above described reaction conditions and led to **11** in 73% yield.

An analogous sequence of reactions was tested in the α-*galacto* series bearing acetates as hydroxyl protecting groups.



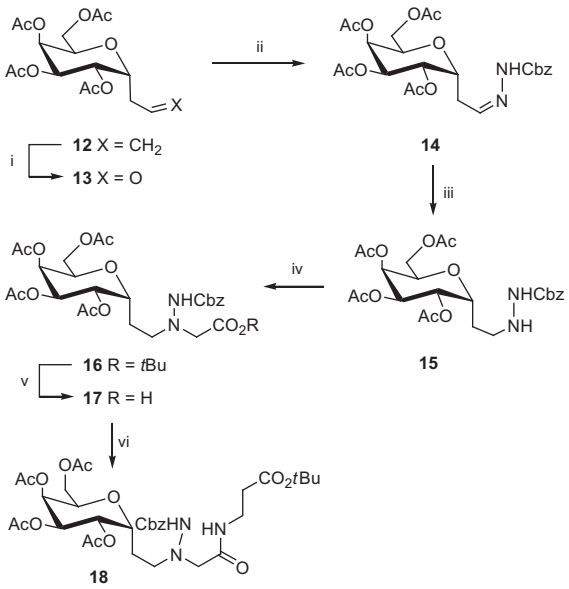
Scheme 1. Reagents and conditions: (i) DIBAL-H, toluene, −78 °C, 2 h, 83%; (ii) BocHN–NH_2, toluene, reflux, 90%; (iii) $NaBH_3CN$, MeOH, CH_2Cl_2, 90%; (iv) $BrCH_2COOR$, toluene, K_2CO_3, 0 °C, reflux for 12 h, R = Et, 82%, R = *i*Pr, 70%.



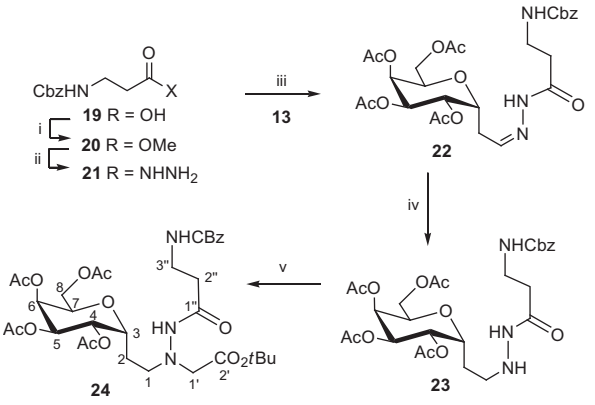
Scheme 2. Reagents and conditions: (i) TFA, CH_2Cl_2, 0 °C, 84%. (ii) *N*-Boc-β-AlaOH, NMM, IBCF, THF, 60%. (iii) $Pd(OH)_2$/C, H_2, CH_2Cl_2, MeOH, 90%. (iv) KOH, MeOH, 80%. (v) H-β-Ala-OMe, NMM, IBCF, THF, 73%.

The *C*-allyl-α-*galacto* derivative **12** prepared by allylation of the commercially available peracetyl-α-D-galactose was obtained as the major compound (α/β: 9/1).[20] Ozonolysis of compound **12** performed in CH_2Cl_2 gave the α-aldehyde **13** in 90% yield (Scheme 3). The latter was treated with benzyloxycarbonyl-hydrazine to give the hydrazone compound **14** in 72% yield.[16] The hydrazine derivative **15** was obtained by reduction of **14** in 70% yield.[17] In this case, N-alkylation was carried out with *tert*-butylbromoacetate giving the new building block **16** in 68% yield.[18]

The chain elongation at the C-terminus of **16** was first explored. Removal of the *tert*-butyl ester was performed by treatment with TFA in MeOH (1/1) leading to the corresponding aza-β-aminoacid **17** in quantitative yield. The coupling reaction between **17** and β-alanine *tert*-butyl ester[21] in the presence of *N*-methyl-morpholine



Scheme 3. Reagents and conditions: (i) O_3, CH_2Cl_2, −78 °C, 90%; (ii) CbzHN–NH_2, toluene, reflux, 72%; (iii) $NaBH_3CN$, MeOH, CH_2Cl_2, 70%; (iv) $BrCH_2COOtBu$, toluene, K_2CO_3, 0 °C, reflux for 12 h, 68% ; (v) TFA/MeOH(1/1), quantitative. (vi) H-β-Ala-O*t*Bu, IBCF, NMM, THF, 50%.



Scheme 4. Reagents and conditions: (i) $SOCl_2$, MeOH, 0 °C then rt, 12 h, 95%. (ii) NH_2–NH_2·H_2O, EtOH, reflux, 75%. (iii) Toluene, reflux, 55%. (iv) $NaBH_3CN$, MeOH, CH_2Cl_2, quantitative. (v) $BrCH_2COOtBu$, toluene, K_2CO_3, 0 °C, reflux, 75%.

and isobutylchloroformate was performed at room temperature and allowed us to obtain compound **18** in 50% yield.

Whatever the experimental conditions (H_2, Pd/C-5%, in MeOH, EtOAc or THF, and atmospheric pressure), used to remove the Cbz protecting group of compound **16**, an inseparable mixture of the desired hydrazine and the amino derivative resulting from the cleavage of the N–N bond was obtained. To overcome this problem, we reasoned that the β-alanine residue could be introduced first. (Scheme 4). Thus *N*-benzyloxycarbonyl-β-alanine hydrazide **21** was prepared starting from the commercially available *N*-benzyloxycarbonyl-β-alanine. Compound **19** was converted to the corresponding methyl ester by treatment with thionyl chloride in methanol to give **20** which was treated with hydrazine monohydrate to provide **21** in 75% yield. The treatment of aldehyde **13** with **21** in refluxing toluene followed by $NaBH_3CN$ reduction allowed us to obtain the expected derivative **23**. Finally, substitution–alkylation of **23** with *tert*-butylbromoacetate afforded the expected aza-β-dipeptide **24**.[22]

New *C*-glycosyl aza-β^3-amino acids have been prepared in a few steps from commercially available 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose and 1,2,3,4,6-penta-*O*-acetyl-D-galactose. Both chiral building blocks have been efficiently coupled at both ends with properly protected β-alanine derivatives. This allowed the synthesis of yet unknown glycosylated aza-β-dipeptides. In view of the recent developments of synthetic molecules able to adopt organized structures, this study demonstrated that these building blocks could be easily expanded and led to a new family of hybrid structures containing glycosylated aza-β-amino acids and β-amino acids.

Acknowledgment

We thank F. Dupire and B. Fernette for their skilful technical assistance.

Supplementary data

Supplementary data (experimental procedures and spectroscopic data of intermediates and final compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03.072.

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16. *General procedure for imine formation*: To a stirred solution of Boc- (or Cbz) carbazate (0.65 mmol) in dry toluene (1.3 mL) was added aldehyde **2** (or **13**) (0.65 mmol). The reaction mixture was heated to 50 °C for 1 h then allowed to cool to room temperature and stirred for 24 h. The solvent was removed under vacuum to give a white solid. The crude product was purified by column chromatography (20% EtOAc/Hexane). Compound **3**: Yield: 90% as a colourless

oil. $[\alpha]_D^{25}$ +2.8 (*c* 1.30, $CHCl_3$). IR (thin film, cm^{-1}): 1711, 3249. ^1H NMR ($CDCl_3$, 250 MHz): δ 1.50 (s, 9H, 3× CH_3), 2.54 (m, 1H, H_{2a}), 2.74 (m, 1H, H_{2b}), 3.28–3.80 (m, 7H, H_3, H_4, H_5, H_6, H_7, 2× H_8), 4.49–4.91 (m, 8H, 4× CH_2Ph), 7.14–7.38 (m, 20H, H_{Ar}), 7.54 (s, 1H, H_1). ^{13}C NMR (C_3D_6O, 62.9 MHz): δ 28.0 (3× CH_3), 35.1 (C_2), 69.4 (C_8), 73.2, 74.7, 74.8, 75.3 (4× CH_2Ph), 77.6 (C_3), 78.9 (C_6), 79.3 ($C(CH_3)_3$), 79.4 (C_7), 81.8 (C_4), 87.3 (C_5), 127.6–128.5 (C_{Ar}), 139.0, 139.1, 139.4 (4× C_{ipso}), 144.0 (C_1), 152.7 (C═O). HRMS (ESI^+) calculated for $C_{41}H_{48}N_2O_7Na$ $[M+Na]^+$: calcd: 703.3354, found:703.3361. Compound **14**: Yield: 72% as a colourless oil. $[\alpha]_D^{25}$ +46.0 (*c* 1.00, $CHCl_3$). IR (thin film, cm^{-1}): 1739, 3466. ^1H NMR ($CDCl_3$, 250 MHz) 1.99, 2.03, 2.08, 2.12 (s, 12H, 4× CH_3), 2.52 (ddd, 1H, J_{1-2a} <1 Hz, J_{2a-3} = 4.7 Hz, J_{gem} = 6.2 Hz, H_{2a}), 2.76 (ddd, 1H, J_{1-2b} <1 Hz, J_{2b-3} = 4.7 Hz, H_{2b}), 4.03 (dd, 1H, J_{7-8a} = 4.4 Hz, J_{gem} = 10.8 Hz, H_{8a}), 4.16 (ddd, 1H, J_{6-7} = 2.9 Hz, J_{7-8b} = 7.3 Hz, H_7), 4.26 (m, 1H, H_{8b}), 4.46 (ddd, 1H, J_{3-4} = 10.6 Hz, H_3), 5.19–5.28 (m, 2H, H_4, H_5), 5.23 (s, 2H, CH_2Ph), 5.43 (pseudo t, 1H, J_{5-6} = 2.7 Hz, H_6), 7.17 (s, 1H, NH), 7.34–7.41 (m, 5H, H_{Ar}), 7.98 (dd, 1H, H_1), 8.31 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 62,9 MHz) δ 20.7, 20.8, 20.9 (4× CH_3), 30.2 (C_2), 61.3 (C_8), 67.4 (CH_2Ph), 67.6, 67.9, 68.1, 69.2 (C_4, C_5, C_6, C_7), 69.8 (C_3), 128.3–128.8 (C_{Ar}), 135.8 (C_{ipso}), 143.9 (C_1), 153.2, 169.8, 169.9, 170.1, 170.7 (5× C═O). HRMS (ESI^+) for $C_{24}H_{30}NaN_2O_{11}$ $[M+Na]^+$: calculated: 545.1742, found: 545.1753.

17. *General procedure for imine reduction*: To a stirred solution of **3** (or **14**) (0.46 mmol) in MeOH/DCM (3/2, 4.5 mL) was added $NaBH_3CN$ (0.55 mmol). The reaction mixture was acidified to pH = 3 by addition of 3 M HCl and stirred for 30 min after which the pH was adjusted to 1. The reaction was stirred until completion (monitored by TLC) then quenched with sat. $NaHCO_3$, filtered and evaporated to dryness. The residue was diluted with EtOAc and washed successively with water and saturated aq. NaCl. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (30% EtOAc/Hexane). Compound **4**: Yield 90% as a colourless oil. $[\alpha]_D^{25}$ +30.6 (*c* 1.10, $CHCl_3$). IR (thin film, cm^{-1}): 1700, 3249, 3330. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.43 (s, 9H, 3× CH_3), 1.64 (m, 1H, H_{2a}), 1.98 (m, 1H, H_{2b}), 2.90–3.05 (m, 2H, 2× H_1), 3.26–3.47 (m, 3H, H_4, H_7, H_{8a}), 3.58–3.75 (m, 4H, H_3, H_5, H_6, H_{8b}), 4.52–4.68 (m, 4H, 2× CH_2Ph), 4.81–4.97 (m, 4H, 2× CH_2Ph), 6.24 (s, 1H, NH), 7.16–7.37 (m, 20H, H_{Ar}). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.3 (3× CH_3), 30.0 (C_2), 49.0 (C_1), 69.0 (C_8), 73.3, 74.9, 75.2, 75.4 (4× CH_2Ph), 78.0 (C_3), 78.5 (C_6), 78.6 (C_7), 80.0 ($C(CH_3)_3$), 82.0 (C_4), 87.2 (C_5), 127.5–128.4 (C_{Ar}), 138.0, 138.1, 138.5 (C_{ipso}), 156.6 (C═O). MS (ES+)**:** *m/z* = 683 [$(M+H)^+$, 52%], 705 [$(M+Na)^+$, 100%]. Anal. calcd for $C_{41}H_{50}N_2O_7$: C, 72.12; H, 7.38; N, 4.10, found: C, 71.92; H, 7.19; N, 4.10. Compound **15**: Yield 70% as a colourless oil. $[\alpha]_D^{25}$ +40.1 (*c* 1.50, $CHCl_3$). I.R (thin film, cm^{-1}): 1750, 3331. ^1H NMR ($CDCl_3$, 250 MHz): 1.64 (m,1H, H_{2a}), 1.84 (m, 1H, H_{2b}), 2.03, 2.04, 2.08, 2.12 (4× s, 12H, 4× CH_3), 2.91–3.07 (m, 2H, 2× H_1), 4.03–4.13 (m, 2H, 2× H_8), 4.26–4.39 (m, 2H, H_3, H_7), 5.14 (s, 2H, CH_2Ph), 5.19–5.27 (m, 2H, H_4, H_5), 5.41 (pseudo t, 1H, J_{5-6} = 2.6 Hz, J_{6-7} = 2.6 Hz, H_6), 6,05 (s, 1H, NH), 6.37 (s, 1H, NH), 7.32–7.39 (m, 5H, H_{Ar}). ^{13}C NMR ($CDCl_3$, 62.9 MHz): 20.8, 20.9, 21.0 (4× CH_3), 24.5 (C_2), 48.4 (C_1), 61.5 (C_8), 67.2 (CH_2Ph), 67.5, 68.0, 68.4, 68.8 (C_4, C_5, C_6, C_7), 70.3 (C_3), 128.3–128.7 (C_{Ar}), 136.1 (C_{ipso}), 157.4, 169.9, 170.1, 170.8 (5× C═O). Anal. calcd for $C_{24}H_{33}N_2O_{10}$: C, 54.96; H, 6.15; N, 5.34, found: C, 54.91; H, 6.36; N, 6.60. HRMS (ESI^+) for $C_{24}H_{33}N_2O_{11}$ $[M+H]^+$: calculated: 525.2079, found: 525.2087.
18. *General procedure for N^2-alkylation*: A solution of **4** (or **15**) (0.31 mmol) in dry toluene (3.0 ml) was cooled to 0 °C. K_2CO_3 (0.31 mmol) and alkyl bromoacetate (0.40 mmol) were successively added. The reaction was stirred for 2 h at 0 °C then refluxed overnight. Filtration and evaporation of the solvent gave the crude product which was purified by column chromatography (20% EtOAc/Hexane). Compound **6**: Yield: 70% as a colourless oil. $[\alpha]_D^{25}$ −1.5 (*c* 1.48, $CHCl_3$). IR (thin film, cm^{-1}): 2977, 1735, 1455. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.27 (d, 6H, $J_{3'-4'}$ = 6 Hz, 6× $H_{4'}$), 1.43 (s, 9H, 3× CH_3), 1.69 (m, 1H, H_{2a}), 2.15 (m, 1H, H_{2b}), 3.01 (m, 1H, H_{1a}), 3.16 (m, 1H, H_{1b}), 3.30 (dd, 1H, J_{3-4} = 8.5 Hz, J_{4-5} = 9.5 Hz, H_4), 3.40–3.45 (m, 2H, H_6, H_7), 3.61–3.73 (m, 6H, $2H_{1'}$, H_3, H_5, 2× H_8), 4.54–4.70 (m, 4H, 2× CH_2Ph), 4.83–4.89 (m, 4H, 2× CH_2Ph), 5.08 (m, 1H, $H_{3'}$), 6.66 (s, 1H, NH), 7.18–7.32 (m, 20H, H_{Ar}). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.3 ($C_{4'}$), 28.7 (3× CH_3), 30.6 (C_2), 53.7 (C_1), 58.2 ($C_{1'}$), 68.7 ($C_{3'}$), 69.4 (C_8), 73.8, 75.2, 75.6, 75.9 (4× CH_2Ph), 77.6 (C_3), 79.1 (C_6) 79.3 (C_7), 80.2 ($C(CH_3)_3$), 89.9 (C_4), 87.6 (C_5), 127.9–128.9 (C_{Ar}), 138.5, 138.6, 138.7, 139.1 (4× C_{ipso}), 155.5 (C═O), 170.9 ($C_{2'}$). HRMS (ESI^+) for $C_{46}H_{59}N_2O_9$ $[M+H]^+$: calculated: 783.4215, found: 783.4243. Compound **16**: Yield 68% as a colourless oil. $[\alpha]_D^{25}$ +41.0 (*c* 1.10, $CHCl_3$). I.R (thin film, cm^{-1}):1749, 3412. ^1H NMR ($CDCl_3$, 250 MHz):1.47 (s, 9H, 3× CH_3), 1.70 (m,1H, H_{2a}), 1.87 (m, 1H, H_{2b}), 2.05, 2.06, 2.07, 2.13 (4× s, 12H, 4× CH_3), 2.92 (m, 1H, H_{1a}), 3,10 (m, 1H, H_{1b}), 3.56–3.62 (m, 2H, 2× $H_{1'}$), 4.06–4.13 (m, 2H, 2× H_8), 4.25 (m, 1H, H_7), 4.44 (m,1H, H_3), 5.14 (s, 2H, CH_2Ph), 5.17 (dd, 1H, J_{4-5} = 9.0 Hz, J_{5-6} = 3.0 Hz, H_5), 5.27 (dd, 1H, J_{3-4} = 5.0 Hz, H_4), 5.41 (m, 1H, H_6), 6.97 (s, 1H, NH), 7.33–7.39 (m, 5H, H_{Ar}). ^{13}C NMR ($CDCl_3$, 62.9 MHz): 21.1, 21.2, (4× CH_3), 24.7 (C_2), 28.5 (3× CH_3), 53.2 (C_1), 59.0 ($C_{1'}$), 62.0 (C_8), 67.3 (CH_2Ph), 67.9 (C_5), 68.4, 68.6, 69.0 (C_4, C_6, C_7), 70.1 (C_3), 82.6 ($C(CH_3)_3$), 128.6–129.0 (C_{Ar}), 136.6 (C_{ipso}), 156.3, 170.2, 170.3, 170.5 (5× C═O), 170.9 ($C_{2'}$). HRMS (ESI^+) for $C_{30}H_{42}Na_1N_2O_{13}$ $[M+H]^+$: calculated: 661.2579, found: 661.2572.
19. NMR data for compound **8**: ^1H NMR (CD_3OD, 400 MHz): δ 1.24 (d, 6H, $J_{3'-4'}$= 6.0 Hz, 6× $H_{4'}$),1.42, 1.43 (2s, 9H, 3× CH_3), 1.59 (m, 1H, H_{2a}), 2.02 (m, 1H, H_{2b}), 2.21 (m, 1H, $H_{2a''}$), 2.45 (m, 1H, $H_{2b''}$), 2.09 (m, 1H, H_{1a}), 3.13 (m, 1H, H_{1b}), 3.17–3.73 (m, 11H, $H_{1a'}$, $H_{1b'}$, H_3, $H_{3a''}$, $H_{3b''}$, H_4, H_5, H_6, H_7, 2× H_8), 4.48–4.69 (m, 4H, 2× CH_2Ph), 4.75–4.96 (m, 4H, 2× CH_2Ph), 5.02 (m, 1H, $H_{3'}$), 7.18–7.31 (m, 20H, H_{Ar}). ^{13}C NMR (CD_3OD, 100 MHz): δ 22.1 ($C_{4'}$), 28.7, 28.8 (3× CH_3), 30.8 (C_2), 35.6 ($C_{2''}$), 38.0 ($C_{3''}$), 54.0 (C_1), 58.9 ($C_{1'}$), 69.6 (C_8), 70.3 ($C_{3'}$), 74.4, 75.8, 76.1, 76.4 (4× CH_2Ph), 77.8 ($C(CH_3)_3$), 78.1 (C_3), 79.8, 79.9 (C_6, C_7), 83.6 (C_4), 88.3 (C_5), 128.7–129.4 (C_{Ar}), 139.4, 139.5, 139.6, 139.9 (C_{ipso}), 158. 2 (C═O), 170.8, 170.9 ($C_{2'}$), 172.5 ($C_{1''}$). HRMS (ESI^+) for $C_{49}H_{64}N_3O_{10}$ $[M+H]^+$: calculated: 854.4586, found: 854.4617.
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22. NMR data for compound **24**: ^1H NMR (CD_3OD, 250 MHz): 1.44 (s, 9H, 3× CH_3), 1.65–1.68 (m, 2H, 2× H_2), 2.01, 2.03, 2.08, 2.10 (s, 12H, 4× CH_3), 2.30–2.36 (m, 2H, 2× H_1), 2.84–2.87 (m, 2H, 2× $H_{2''}$), 3.39–3.44 (m, 2H, 2× $H_{3''}$), 3.56–3.58 (m, 2H, 2× $H_{1'}$), 4.01–4.42 (m, 4H, H_3, H_7, 2× H_8), 5.07 (s, 2H, CH_2Ph), 5.01–5.23 (m, 2H, H_4, H_5), 5.37 (s, 1H, H_6), 7.23–7.48 (m, 5H, H_{Ar}). ^{13}C NMR (CD_3OD, 100 MHz): 20.5, 20.6, 20.7, 20.8 (4× CH_3), 25.1 (C_2), 28.4 (3× CH_3), 35.6 ($C_{2''}$), 38.4 ($C_{3''}$), 53.6 (C_1), 59.7 ($C_{1'}$), 62.6 (C_8), 67.4 (CH_2Ph), 69.1 (C_6), 69.4 (C_4), 69.6 (C_5), 69.7 (C_7), 71.1 (C_3), 82.8 ($C(CH_3)_3$), 128.8–129.5 (C_{Ar}), 138.3 (C_{ipso}), 158.7 (C═O), 170.8 ($C_{2'}$), 171.5, 171.6, 171.9, 172.3 (4× C═O), 172.5 ($C_{1''}$). HRMS (ESI^+) for $C_{33}H_{47}Na_1N_3O_{14}$ $[M+Na]^+$: calculated: 732.2950, found: 732.2952