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Hexafluoroacetone as Protecting and Activating Reagent. A New Approach to *N*-linked Glycopeptoids

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Summary. A preparatively simple synthesis of *N*-linked glycopeptoids starting from iminodiacetic acid and glycosylamines, using hexafluoroacetone as protecting and activating reagent is described.

Keywords. Iminodiacetic acid; Hexafluoroacetone; Dielectrophile; Glycosylamines; *N*-Glycosylation; Peptoids; Glycopeptoids.

Introduction

Peptide drugs are a fastly growing class of therapeutics [1]. However, proteolytic instability, low lipophilicity, and lack of transport systems are the major drawbacks, restricting their application considerably. In general, cell membranes resist passage of most peptides. Consequently, peptides are rapidly degradated and excreted *via* liver and kidney. The high conformational flexibility of peptides creates another problem. Bioactive peptides often bind to different receptor sites causing undesired side effects [2, 3]. Several strategies have been developed to overcome these problems, including the application of peptidomimetics [4, 5] and glycopeptides [6, 7] as drug candidates.

The construction of peptoids [8] (Scheme 1), a new class of non-natural peptides, added a new facette to peptide modification [9]. Peptoids are *N*-alkyl- and *N*-aryl-substituted oligoglycines, having no chiral centers [10]. Other characteristics are high conformational flexibility, high structural diversity, and improved proteolytic stability. Comparison of the peptide chain with the peptoid chain (Scheme 1) shows that the direction of the peptide bond has to be reversed (retro-sequence) in order to provide the same relative arrangement of the side-chain

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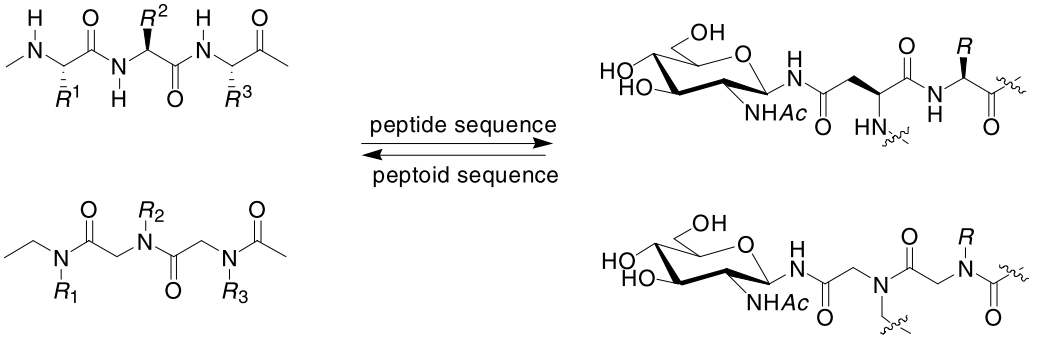


Scheme 1

residues and carbonyl groups. Helical peptoid structures are favored when bulky *N*-alkyl side-chains are present. Interestingly, these helices are not stabilized by hydrogen bonds [1a, 11]. Noteworthy, the peptoid approach is amenable to solid-phase synthesis [8a, 12] which provides libraries of high structural diversity.

Roy et al. were the first to combine the advantages of peptoid and glycoconjugate chemistry. They synthesized a series of *N*-linked [13] and *O*-linked glycopeptoids [14] and used them as building blocks for the construction of HIV-1 protease inhibitors [15] and T_N-antigen glycopeptidomimetic clusters [16]. Recently, *Kessler et al*. reported on a stereoselective synthesis of *C*-glycosylated peptoids [17].

The first example of this new class of ''non-natural biooligomers'', an asparagine linked *N*-acetyl glucosaminide mimic, has been synthesized by *Roy et al.* [13a] *via* a *N*-glycosylated tripeptoid. The latter was obtained in six steps starting from *tert*-butyl bromoacetate and *N*-acetyl glucosaminide. The submonomer solid-phase synthesis does not apply *N*-substituted glycine monomers. Instead, bromoacetyl building blocks are coupled to the growing peptoid chain and then subjected to a nucleophilic displacement reaction of the bromide by a primary amine carrying the side-chain substituent. Protection of the amino group is not necessary.

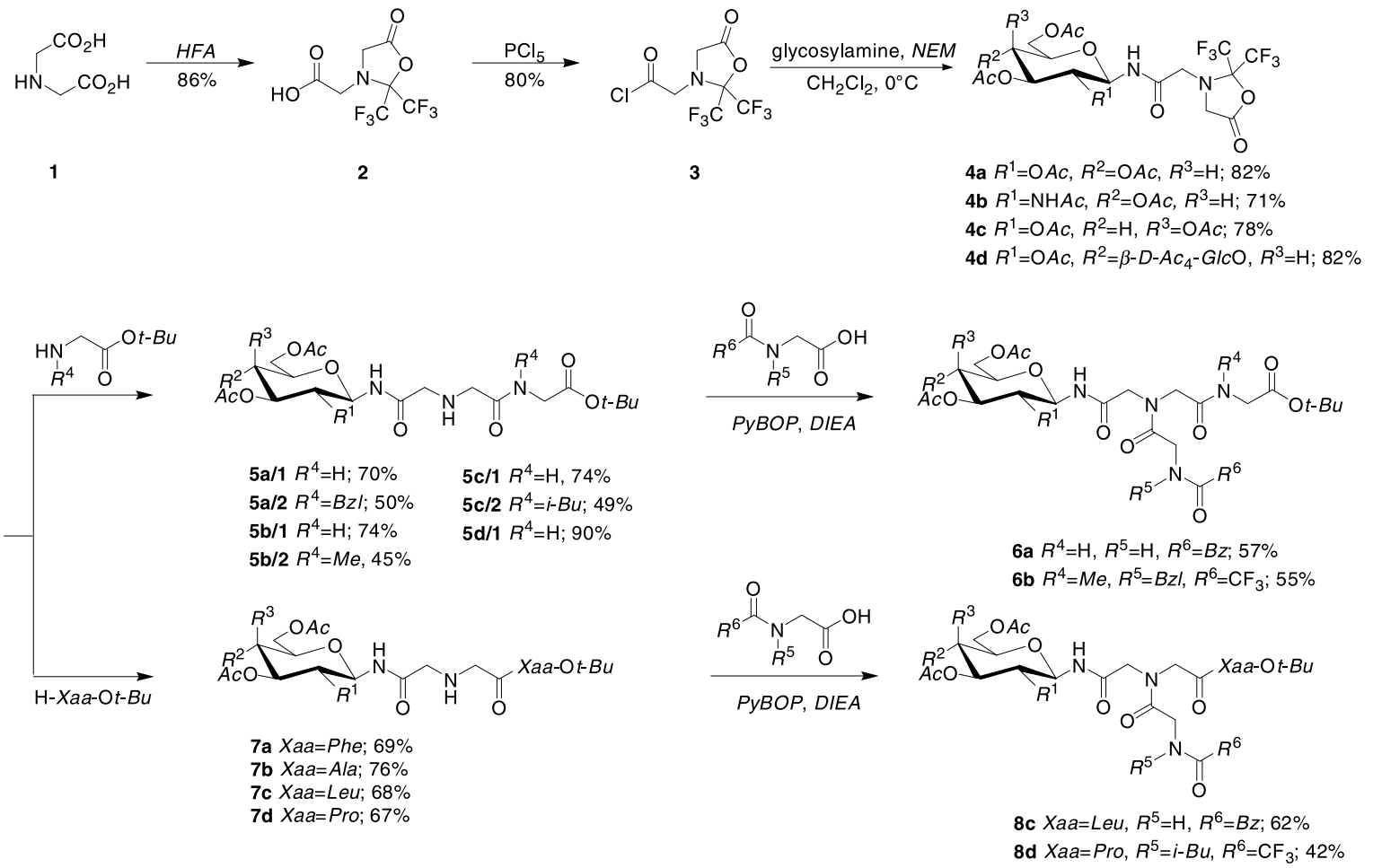
In contrast, in the *Fmoc*/O^t*Bu* strategy suitably protected *N*-substituted glycine derivatives are coupled to polymer-bound NH*R* groups using *PyBOP* or *PyBrOP* [8b].

Herein we describe a new, preparatively simple access to *N*-linked glycopeptoids using hexafluoroacetone as protecting and activating reagent.

Results and Discussion

On application of hexafluoroacetone as protecting and activating agent, *N*-glycosylated tripeptoids can be obtained in five steps with an overall yield of 12–23%, starting from iminodiacetic acid (**1**, Scheme 2).

First, **1** is transformed into lactone **2** on reaction with hexafluoroacetone in dimethylsulfoxide (*DMSO*) or dimethylformamide (*DMF*) at room temperature [18]. This process includes simultaneous functionalization of the imino and one of the carboxy groups. The second carboxy group remains unaffected. The lactone moiety represents an activated ester. In a second step the exocyclic carboxy group can be transformed into an acid chloride. Noteworthy, treatment of **2** with


HFA
86%
PCl5
80%
glycosylamine, NEM
CH2Cl2, 0°C
1
2
3
4a R1=OAc, R2=OAc, R3=H; 82%
4b R1=NHAc, R2=OAc, R3=H; 71%
4c R1=OAc, R2=H, R3=OAc; 78%
4d R1=OAc, R2=β-D-Ac4-GlcO, R3=H; 82%
5a/1 R4=H; 70%
5a/2 R4=Bzl; 50%
5b/1 R4=H; 74%
5b/2 R4=Me, 45%
5c/1 R4=H, 74%
5c/2 R4=i-Bu; 49%
5d/1 R4=H; 90%
PyBOP, DIEA
6a R4=H, R5=H, R6=Bz; 57%
6b R4=Me, R5=Bzl, R6=CF3; 55%
H-Xaa-Ot-Bu
7a Xaa=Phe; 69%
7b Xaa=Ala; 76%
7c Xaa=Leu; 68%
7d Xaa=Pro; 67%
8c Xaa=Leu, R5=H, R6=Bz; 62%
8d Xaa=Pro, R5=i-Bu, R6=CF3; 42%

Scheme 2

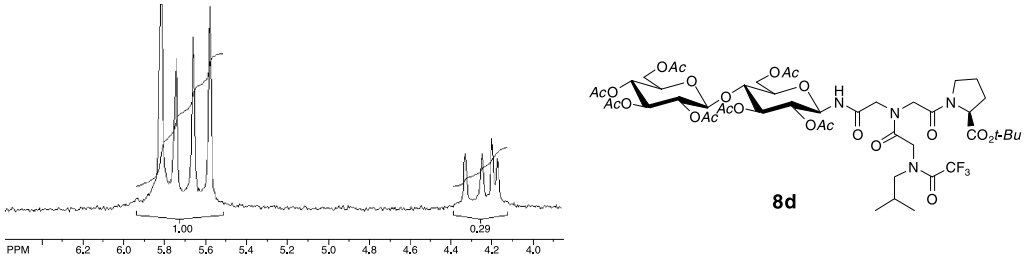


Fig. 1. ^{19}F NMR spectra ($CDCl_3$, 282 MHz) of compound **8d** at 300 K

phosphorus pentachloride gives better yields than treatment with thionyl chloride. **3** represents a dielectrophile. Consequently, a sequence of two regioselective acylation steps can be performed. On treatment with relatively weak nucleophiles (1 equiv.) like glycosylamines in the presence of a *tert*-base, the more reactive acid chloride moiety reacts regioselectively to give the *N*-glycosylated, α-carboxy activated glycine derivative **4**. NMR and TLC of the crude products indicate clearly that only the β-anomers are formed. The β-anomers can be identified by a characteristic coupling constant $^3J_{1,2} = 9.3 \pm 0.3$ Hz. We applied compounds **4** as acyl transfer reagents for amino acid esters and amides, providing dipeptoids and dipeptides in good yields, respectively. Yields and reaction rate depend on the sterical demand of the nucleophiles (reaction rate: glycine (70–90%) > α-amino acid (68–76%) > *N*-alkylated glycine derivatives (45–50%)). In the case of hexafluoroacetone protected amino acids the cleavage of the lactone moiety is always coupled with the deprotection of the α-amino group (**4** $\rightarrow$ **5**). Therefore, elongation of the peptoid chain can be continued in *N*-terminal position without the need of an extra deprotection step to give the *N*-glycosylated tripeptoids **6** and peptide/peptoid hybrids **8**, respectively. Compounds **5**–**8** show complex ^{1}H NMR spectra due to the presence of mixtures of rotamers, which can be observed in the case of secondary amides. In the trifluoroacetyl protected *N*-glycosylated tripeptoid **8d** three stereogenic centers are present giving rise to eight rotational isomers, which indeed can be found in the ^{19}F NMR spectrum (Fig. 1). The structures of the newly synthesized compounds are unequivocally confirmed by NMR and mass spectrometry.

The readily available *N*-glycosylated peptoid fragments are valuable building blocks for the synthesis of glycopeptoids and glycopeptide mimetics in solution and on solid phase. Peptoids represent a new class of lead structures for the therapy of pathological events.

Experimental

Solvents were purified and dried prior to use. Reagents were used as purchased. TLC was performed on Silica Gel 60 F_{254} (Merck) with detection by UV light or phosphomolybdic acid/ceric sulphate in 5% aqueous sulfuric acid followed by heating. Flash chromatography was performed using silica gel (32–63 µm) with solvent systems given in the text. Melting points (uncorrected) were determined on a *Boetius* heating table. Optical rotation indices were measured using a Schmidt & Haensch Polartronic-D polarimeter in a 5 cm cell. ^{1}H (200 MHz, 300 MHz, 400 MHz, 600 MHz), ^{13}C (50 MHz, 75 MHz, 100 MHz, 150 MHz), and ^{19}F (188 MHz, 282 MHz) NMR spectra were recorded on Varian Gemini 200, Varian Gemini 300, Bruker DRX 400, and Bruker DRX 600 spectrometers. *TMS* was used as

reference for ^{1}H and ^{13}C NMR spectra (internal), and CF_3COOH for ^{19}F NMR spectra (external). IR spectra were obtained with a FTIR spectrometer (Genesis ATI Mattson/Unicam). Mass spectra were recorded on a Bruker Daltonics APEX II ESI-FT-ICR spectrometer or on a Finnigan ZAB-HSQ spectrometer (FAB-matrix: 3-*NBA*).

Synthesis of N-Glycosylated Peptoids

Protocol 1: A solution of the acid chloride **3** (1 equiv.) in dichloromethane (*DCM*) (5 cm^3 per 1 mmol) was cooled to 0°C. Over a period of 30 min a freshly prepared solution of the corresponding *O*-peracetylated *β-D*-glycosylamine (1 equiv.) and *N*-ethylmorpholine (*NEM*) (1 equiv.) in *DCM* (5 cm^3 per 1 mmol) were added. After vigorous stirring for 1 h at 0°C, *DCM* (20 cm^3 per 1 mmol) was added. The organic phase was extracted with diluted citric acid (10%) and sat. NaCl solution (10 cm^3 per 1 mmol). After drying with $MgSO_4$, the organic solvent was evaporated and the residue was purified by flash chromatography.

Protocol 2: A suspension of the corresponding amino acid hydrochloride (1.2 equiv.) in ethyl acetate: 2-propanol (1:1, 5 cm^3 per 1 mmol) was stirred with *NEM* (1.2 equiv.) for 15 min. Then the corresponding *HFO* (2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one, 1 equiv.) was added. The mixture was stirred at room temperature until TLC analysis showed complete consumption of the *HFO* (1–4d). After evaporation of the solvent, the residue was purified by flash chromatography.

Protocol 3: A solution of a *N*-terminal protected glycine derivative (1.2 equiv.) in *DMF* (5 cm^3 per 1 mmol) was stirred for 3 min after addition of diisopropylethylamine (*DIEA*) (2.4 equiv.) and benzotriazole-1-yloxytrispyrrolidinophosphonium hexafluorophosphate (*PyBOP*) (1.2 equiv.). Then the glycosylated dipeptide ester (1.0 equiv.) was added and the reaction mixture was stirred for 18 h at room temperature. The solvent was evaporated *in vacuo* and the residue was redissolved in ethyl acetate (30 cm^3). The organic phase was extracted with diluted citric acid (10%, 10 cm^3), sat. $NaHCO_3$ (10 cm^3), and sat. NaCl solution (10 cm^3), and finally dried with $MgSO_4$. After removal of the organic solvent *in vacuo*, the crude product was purified by flash chromatography.

N-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-2-[5-oxo-2,2-bis(trifluoromethyl)-1,3-oxazolidin-3-yl]acetamide (**4a**, $C_{21}H_{24}F_6N_2O_{12}$)

Compound **3** (3.18 g, 10.6 mmol) and *Ac*$_4$-*β-D-Glc*-NH_2 (3.68 g, 10.6 mmol) were reacted due to protocol 1. Purification by flash chromatography (ethyl acetate:petroleum ether = 1:1, $R_f = 0.32$). Yield 5.32 g (82%), colorless foam; $[\alpha]_D = +21°\ cm^3\ g^{-1}\ dm^{-1}$ ($c = 1.3$, *DCM*); ^{1}H NMR ($CDCl_3$, 300 MHz, COSY): $\delta = 2.02$, 2.03, 2.04, 2.07 (4s, 4O*Ac*), 3.66 (d, 1H, $J = 16.8$ Hz, CH_2^{Nasn}), 3.73 (d, 1H, $J = 16.8$ Hz, CH_2^{Nasn}), 3.76 (s, CH_2^{Nasn}), 3.81 (m, 5-H), 4.09 (dd, $J = 2.1$, 12.6 Hz, 6-H_a), 4.28 (dd, $J = 4.5$, 12.6 Hz, 6-H_b), 4.93 (dd, $J = 9.6$, 9.6 Hz, 2-H), 5.07 (dd, $J = 9.3$, 9.9 Hz, 4-H), 5.22 (dd, $J = 9.3$, 9.3 Hz, 1-H), 5.32 (dd, $J = 9.6$, 9.6 Hz, 3-H), 7.07 (d, $J = 9.0$ Hz, 1-NH) ppm; ^{19}F NMR ($CDCl_3$, 282 MHz): $\delta = 1.54$ (m, 3F), 1.63 (m, 3F) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz, HETCOR): $\delta = 20.92$, 21.02, 21.71 (4O*Ac*), 49.88, 51.69 ($2CH_2^{Nasn}$), 62.31 (6-CH_2), 68.80 (4-CH), 71.16 (2-CH), 73.15 (3-CH), 74.37 (5-CH), 78.72 (1-CH) 90.36 (sept, $J = 33$ Hz), 121.57 (q, $J = 291$ Hz), 166.50, 168.08, 170.32, 170.58, 171.34, 171.52 ppm; IR (KBr): $\bar{\nu} = 1849$, 1753, 1711, 1522 cm^{-1}; MS (FAB): $m/z = 611.1$ $[M + H]^+$.

tert-Butyl N-{2-Oxo-2-[(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)amino]ethyl}glycyl-glycinate (H-N*asn*(*Ac*$_4$-*β-D-Glc*)-*Gly*-O^t*Bu*, **5a**/**1**, $C_{24}H_{37}N_3O_{13}$)

HCl*H-*Gly*-O^t*Bu* (148 mg, 0.88 mmol) and **4a** (450 mg, 0.74 mmol) were reacted due to protocol 2. Reaction time: 18 h. Purification by flash chromatography (*DCM*:*Me*OH = 10:1, $R_f = 0.40$). Yield 300 mg (70%), colorless foam; $[\alpha]_D = +7°\ cm^3\ g^{-1}\ dm^{-1}$ ($c = 1.3$, *DCM*); ^{1}H NMR ($CDCl_3$,

600 MHz, COSY): $\delta = 1.49$ (s, 9H, CH_3^{tBu}), 2.02, 2.04, 2.05, 2.08 (4s, 4OA*c*), 3.27–3.38 (m, $2CH_2^{Nasn}$), 3.83 (m, 5-H), 3.97 (dd, 1H, $J = 5.7$, 18.0 Hz, CH_2^{Gly}), 4.02 (dd, 1H, $J = 5.7$, 18.0 Hz, CH_2^{Gly}), 4.10 (dd, $J = 1.8$, 12.3 Hz, 6-H_a), 4.30 (dd, $J = 4.5$, 12.3 Hz, 6-H_b), 4.98 (dd, $J = 9.6$, 9.6 Hz, 2-H), 5.07 (dd, $J = 9.9$, 9.6 Hz, 4-H), 5.25 (dd, $J = 9.3$, 9.6 Hz, 1-H), 5.32 (dd, $J = 9.6$, 9.6 Hz, 3-H), 7.12 (br.t, $J = 5.7$ Hz, NH^{Gly}), 7.64 (d, $J = 9.3$ Hz, 1-NH) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz, HETCOR): $\delta = 20.65$ (2OA*c*), 20.78 (2OA*c*), 28.21 (CH_3^{tBu}), 41.47 (CH_2^{Gly}), 52.43, 52.57 ($2CH_2^{Nasn}$), 61.85 (6-CH_2), 68.36 (4-CH), 71.02 (2-CH), 72.90 (3-CH), 73.81 (5-CH), 78.11 (1-CH), 82.54 (C^{tBu}), 169.42, 169.68, 169.95, 170.76, 170.96, 171.24, 171.69 ppm; IR (KBr): $\bar{\nu} = 3500$–3300, 1750, 1662, 1534 cm^{-1}; HRMS (ESI): calcd. for $C_{24}H_{38}N_3O_{13}$ ($M + H^+$) 576.23991, found 576.23939.

tert-Butyl N-{2-Oxo-2-[(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)amino]ethyl}glycyl-phenylalaninate (H-N*asn*(*Ac*$_4$-β-*D-Glc*)-*Phe*-O^t*Bu*, **7a**, $C_{31}H_{43}N_3O_{13}$)

HCl*H-*Phe*-O^t*Bu* (410 mg, 1.59 mmol) and **4a** (809 mg, 1.33 mmol) were reacted due to protocol 2. Reaction time: 2d. Purification by flash chromatography (ethyl acetate, $R_f = 0.25$). Yield 613 mg (69%), colorless foam; $[\alpha]_D = +24^\circ\ cm^3\ g^{-1}\ dm^{-1}$ ($c = 1.1$, *DCM*); ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 1.42$ (s, 9H, CH_3^{tBu}), 2.00 (s, OA*c*), 2.02 (s, 2OA*c*), 2.05 (s, OA*c*), 3.00–3.27 (m, CH_2^{Phe}, $2CH_2^{Nasn}$), 3.83 (ddd, $J = 2.2$, 4.4, 9.9 Hz, 5-H), 4.08 (dd, $J = 2.1$, 12.3 Hz, 6-H_a), 4.30 (dd, $J = 4.5$, 12.3 Hz, 6-H_b), 4.78 (m, CH^{Phe}), 4.92 (dd, $J = 9.6$, 9.6 Hz, 2-H), 5.07 (dd, $J = 9.6$, 9.9 Hz, 4-H), 5.25 (dd, $J = 9.6$, 9.3 Hz, 1-H), 5.31 (dd, $J = 9.6$, 9.3 Hz, 3-H), 6.96 (d, $J = 8.0$ Hz, NH^{Phe}), 7.14–7.32 (m, 5H, arom), 7.53 (d, $J = 9.6$ Hz, 1-NH) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 20.67$, 20.75, 20.81 (4OA*c*), 28.09 (CH_3^{tBu}), 38.05 (CH_2^{Phe}), 52.36, 52.49 ($2CH_2^{Nasn}$), 53.43 (CH^{Phe}), 61.80 (6-CH_2), 68.27, 70.84, 72.88, 73.75 (2,3,4,5-CH), 78.00 (1-CH), 82.51 (C^{tBu}), 127.10, 128.57, 129.51, 136.46 (arom), 169.66, 169.95, 170.07, 170.65, 170.93, 170.99, 171.68 ppm; IR (KBr): $\bar{\nu} = 3500$–3300, 1749, 1668, 1521 cm^{-1}; HRMS (ESI): calcd. for $C_{31}H_{44}N_3O_{13}$ ($M + H^+$) 666.28687, found 666.28675.

tert-Butyl N-{2-Oxo-2-[(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)amino]ethyl}glycyl-N-benzylglycinate (H-N*asn*(*Ac*$_4$-β-*D-Glc*)-N*phe*-O^t*Bu*, **5a**/**2**, $C_{31}H_{43}N_3O_{13}$)

H-N*phe*-O^t*Bu* (240 mg, 1.09 mmol) and **4a** (555 mg, 0.91 mmol) were reacted in ethyl acetate (5 cm^3) due to protocol 2. Reaction time: 4d. Purification by flash chromatography (gradient elution: ethyl acetate:petroleum ether = 2:1 → 8:1, $R_f = 0.35$). Yield 300 mg (50%), foam; $[\alpha]_D = +2^\circ\ cm^3\ g^{-1}\ dm^{-1}$ ($c = 1.1$, *DCM*); ^{1}H NMR ($CDCl_3$, 400 MHz, 300 K, COSY): rotational isomers, ratio: 3:2, $\delta = 1.42$ (s, $CH_3^{tBu}{}_{min}$), 1.47 (s, $CH_3^{tBu}{}_{maj}$), 1.91–2.08 (several s, OA*c*), 3.27–3.63 (CH_2^{Nasn}), 3.74 (d, $J = 18.4$ Hz, $CH_2^{Nphe}{}_{min}$), 3.82 (d, $J = 18.4$ Hz, $CH_2^{Nphe}{}_{min}$), 3.83 (m, 5-H), 3.96 (d, $J = 17.2$ Hz, $CH_2^{Nphe}{}_{maj}$), 4.02 (d, $J = 17.2$ Hz, $CH_2^{Nphe}{}_{maj}$), 4.06–4.11 (m, 6-H_a), 4.25–4.31 (m, 6-H_b), 4.51 (d, $J = 18.2$ Hz, CH_2Ph_{maj}), 4.55 (d, $J = 18.2$ Hz, CH_2Ph_{maj}), 4.62 (d, $J = 14.8$ Hz, CH_2Ph_{min}), 4.68 (d, $J = 14.8$ Hz, CH_2Ph_{min}), 4.94–5.11 (m, 2,4-H), 5.23–5.34 (m, 1,3-H), 7.18–7.39 (m, H arom), 8.06 (d, $J = 9.9$ Hz, 1-NH_{maj}), 8.10 (d, $J = 9.9$ Hz, 1-NH_{min}) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, 300 K, HMQC): $\delta = 20.5$–20.8 (OA*c*), 27.96 ($CH_3^{tBu}{}_{min}$), 28.07 ($CH_3^{tBu}{}_{maj}$), 47.97 ($CH_2^{Nphe}{}_{maj}$), 48.37 ($CH_2^{Nphe}{}_{min}$), 50.33 (CH_2^{Nasn}), 50.43 (CH_2Ph_{min}), 50.94 (CH_2Ph_{maj}), 52.64 (CH_2^{Nasn}), 61.74 (6-CH_2), 68.19 (4-CH), 70.77 (2-CH), 72.93 (3-CH), 73.69 (5-CH), 77.80 (1-CH), 82.09 ($C^{tBu}{}_{maj}$), 82.94 ($C^{tBu}{}_{min}$), 126.72, 127.84, 128.10, 128.61, 128.76, 129.15, 135.42, 136.14, 167.66, 168.05, 169.55, 169.61, 170.30, 170.63, 171.02, 171.27, 172.15 ppm; IR (KBr): $\bar{\nu} = 3500$–3300, 1747, 1657 cm^{-1}; HRMS (ESI): calcd. for $C_{31}H_{44}N_3O_{13}$ ($M + H^+$) 666.28687, found 666.28664.

tert-Butyl N-Benzoylglycyl-N-{2-oxo-2-[(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-amino]ethyl}glycylglycinate (*Bz-Gly*-N*asn*(*Ac*$_4$-β-*D-Glc*)-*Gly*-O^t*Bu*, **6a**, $C_{33}H_{44}N_4O_{15}$)

Bz-Gly-OH (65 mg, 0.36 mmol) and **5a**/**1** (173 mg, 0.30 mmol) were reacted due to protocol 3. Purification by flash chromatography ($CHCl_3$:*Me*OH = 15:1, $R_f = 0.27$). Yield 127 mg (57%), colorless

crystals; mp 102–103°C; $[\alpha]_D = -36^\circ\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.2$, *DCM*); ^{1}H NMR ($CDCl_3$, 600 MHz, 300 K, COSY): rotational isomers, ratio: 10:3; $\delta = 1.43$ (s, $CH_3^{tBu}{}_{maj}$), 1.45 (s, $CH_3^{tBu}{}_{min}$), 1.97 (s, O*Ac* $_{min}$), 1.98 (s, O*Ac* $_{min}$), 1.99 (s, O*Ac* $_{maj}$), 2.02 (s, O*Ac* $_{min+maj}$), 2.03 (s, O*Ac* $_{maj}$), 2.04 (s, O*Ac* $_{min+maj}$), 3.63 (dd, $J = 4.8$, 18.0 Hz, $CH_2^{Gly}{}_{maj}$), 3.72 (d, $J = 16.2$ Hz, $CH_2^{Nasn}{}_{maj}$), 3.80 (m, 5-H $_{min}$), 3.82 (m, 5-H $_{maj}$), 3.87 (dd, $J = 5.4$, 18.0 Hz, $CH_2^{Gly}{}_{maj}$), 3.95 (dd, $J = 5.4$, 18.0 Hz, $CH_2^{Gly}{}_{min}$), 3.99 (dd, $J = 4.8$, 18.0 Hz, $CH_2^{Gly}{}_{min}$), 4.01 (d, $J = 18.0$ Hz, $CH_2^{Nasn}{}_{maj}$), 4.07–4.24 (m, 6-H_2, $CH_2^{Nasn}{}_{min}$ (4H), $CH_2^{Gly}{}_{min}$ (2H), $CH_2^{Nasn}{}_{maj}$ (1H), $CH_2^{Gly}{}_{maj}$ (1H)), 4.33 (d, 1H, $J = 18.0$ Hz, $CH_2^{Nasn}{}_{maj}$), 4.46 (dd, 1H, $J = 6.0$, 16.8 Hz, $CH_2^{Gly}{}_{maj}$), 5.00–5.10 (m, 2,4-H), 5.24–5.31 (m, 1,3-H), 7.10 (br.t, $J = 5.4$ Hz, $NH^{Gly}{}_{min}$), 7.34 (br.t, $J = 4.8$ Hz, $NH^{Gly}{}_{min}$), 7.41 (t, $J = 7.8$ Hz, $H^{meta}{}_{min}$), 7.44 (t, $J = 7.8$ Hz, $H^{meta}{}_{maj}$), 7.48–7.52 (m, H^{para}), 7.54 (br.t, $J = 5.4$ Hz, $NH^{Gly}{}_{maj}$), 7.57 (br.t, $J = 5.4$ Hz, $NH^{Gly}{}_{maj}$), 7.81 (d, $J = 7.8$ Hz, $H^{ortho}{}_{min}$), 7.85 (d, $J = 7.8$ Hz, $H^{ortho}{}_{maj}$), 8.82 (d, $J = 9.6$ Hz, 1-NH $_{maj}$), 9.47 (d, $J = 9.3$ Hz, 1-NH $_{min}$) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz, 300 K): $\delta = 20.71$, 20.86, 21.07 (O*Ac*), 28.17 (CH_3^{tBu}), 41.71 ($CH_2^{Gly}{}_{min}$), 42.11 ($2CH_2^{Gly}{}_{maj}$), 42.31 ($CH_2^{Gly}{}_{min}$), 53.00 ($CH_2^{Nasn}{}_{maj}$), 53.10 ($CH_2^{Nasn}{}_{min}$), 53.28 ($CH_2^{Nasn}{}_{min}$), 54.81 ($CH_2^{Nasn}{}_{maj}$), 61.82 (6-$CH_2{}_{min}$), 62.07 (6-$CH_2{}_{maj}$), 68.23 (4-CH $_{min}$), 68.42 (4-CH $_{maj}$), 70.75 (2-CH $_{maj}$), 70.96 (2-CH $_{min}$), 73.12 (3-CH $_{maj}$), 73.46 (3-CH $_{min}$), 73.76 (5-CH $_{maj}$), 73.90 (5-CH $_{min}$), 78.13 (1-CH $_{maj}$), 78.27 (1-CH $_{min}$), 82.60 (C^{tBu}), 127.26, 128.74, 131.99, 133.48 ($_{maj}$), 133.60 ($_{min}$), 167.29, 167.62, 168.70, 168.86, 169.03, 169.15, 169.62, 169.69, 169.75, 169.95, 170.06, 170.14, 170.29, 170.53, 170.72, 170.89, 171.49 ppm; IR (KBr): $\bar{\nu} = 3600$–3300, 1754, 1652, 1535 cm^{-1}; MS (FAB): $m/z = 737.3$ $[M + H]^+$.

N-(3,4,6-Tri-O-acetyl-2-acetamido-2-deoxy-β-D-glucopyranosyl)-2-[5-oxo-2,2-bis(trifluoromethyl)-1,3-oxazolidin-3-yl]acetamide (**4b**, $C_{21}H_{25}F_6N_3O_{11}$)

Compound **3** (1.89 g, 6.30 mmol) and *Ac*$_3$-β-*D*-*Glc*N*Ac*-NH_2 (2.18 g, 6.30 mmol) were reacted due to protocol 1. Purification by flash chromatography (ethyl acetate:petroleum ether = 5:1, $R_f = 0.40$). Yield 2.72 g (71%), foam; $[\alpha]_D = +11^\circ\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 2.5$, *DCM*); ^{1}H NMR (*DMSO*-d_6, 400 MHz, COSY): $\delta = 1.74$ (s, N*Ac*), 1.91, 1.97, 2.00 (3s, 3O*Ac*), 3.69 (d, 1H, $J = 16.8$ Hz, CH_2^{Nasn}), 3.74 (d, 1H, $J = 16.8$ Hz, CH_2^{Nasn}), 3.86 (ddd, $J = 2.1$, 4.5, 9.9 Hz, 5-H), 3.94 (m, 2-H), 3.97 (dd, $J = 2.1$, 12.6 Hz, 6-H_a), 4.15 (s, CH_2^{Nasn}), 4.18 (dd, $J = 4.5$, 12.6 Hz, 6-H_b), 4.83 (dd, $J = 9.6$, 9.9 Hz, 4-H), 5.12 (dd, $J = 9.9$, 9.9 Hz, 3-H), 5.18 (dd, $J = 9.6$, 9.3 Hz, 1-H), 7.95 (d, $J = 9.3$ Hz, NH*Ac*), 8.71 (d, $J = 9.3$ Hz, 1-NH) ppm; ^{19}F NMR (*DMSO*-d_6, 282 MHz): $\delta = 2.21$ (q, 3F, $J = 8.0$ Hz), 2.50 (q, 3F, $J = 8.0$ Hz) ppm; ^{13}C NMR (*DMSO*-d_6, 100 MHz, HMQC): $\delta = 20.28$, 20.31, 20.43 (3O*Ac*), 22.33 (NH*Ac*), 48.31, 48.76 ($2CH_2^{Nasn}$), 52.07 (2-CH), 61.74 (6-CH_2), 68.36 (4-CH), 72.40 (5-CH), 73.12 (3-CH), 78.02 (1-CH), 89.41 (sept, $J = 33$ Hz), 120.72 (q, $J = 292$ Hz), 167.47, 167.56, 169.26, 169.49, 169.53, 169.95 ppm; IR (KBr): $\bar{\nu} = 3400$, 1847, 1749, 1662, 1524 cm^{-1}; MS (FAB): $m/z = 610.1$ $[M + H]^+$.

tert-Butyl N-{2-Oxo-2-[(3,4,6-tri-O-acetyl-2-acetamido-2-deoxy-β-D-glucopyranosyl)-amino]ethyl}glycylglycinate (H-N*asn*(*Ac*$_3$-β-*D*-*Glc*N*Ac*)-*Gly*-O^t*Bu*, **5b**/**1**, $C_{24}H_{38}N_4O_{12}$)

HCl*H-*Gly*-O^t*Bu* (152 mg, 0.91 mmol) and **4b** (436 mg, 0.72 mmol) were reacted due to protocol 2. Reaction time: 18 h. Purification by flash chromatography (*DCM*:*Me*OH = 10:1, $R_f = 0.32$). Yield 305 mg (74%), foam; $[\alpha]_D = -11^\circ\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.1$, DCM); ^{1}H NMR ($CDCl_3$, 300 MHz, COSY): $\delta = 1.44$ (s, 9H, CH_3^{tBu}), 1.90 (s, N*Ac*), 2.01, 2.02, 2.05 (3s, 3O*Ac*), 3.25 (d, 1H, $J = 16.7$ Hz, CH_2^{Nasn}), 3.28 (s, CH_2^{Nasn}), 3.33 (d, 1H, $J = 16.7$ Hz, CH_2^{Nasn}), 3.79 (ddd, $J = 2.1$, 4.5, 9.6 Hz, 5-H), 3.91 (dd, 1H, $J = 5.8$, 17.8 Hz, CH_2^{Gly}), 3.99 (dd, 1H, $J = 5.8$, 17.8 Hz, CH_2^{Gly}), 4.07 (dd, $J = 2.1$, 12.6 Hz, 6-H_a), 4.12 (m, 2-H), 4.24 (dd, $J = 4.5$, 12.6 Hz, 6-H_b), 5.04 (dd, $J = 9.3$, 9.9 Hz, 4-H), 5.10 (dd, $J = 9.6$, 9.3 Hz, 1-H), 5.13 (dd, $J = 9.9$, 9.3 Hz, 3-H), 6.73 (d, $J = 9.0$ Hz, NH*Ac*), 7.73 (br.t, $J = 5.8$ Hz, NH^{Gly}), 8.12 (d, $J = 9.0$ Hz, 1-NH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz, HETCOR): $\delta = 20.67$, 20.76, 20.81 (3O*Ac*), 23.11 (NH*Ac*), 28.15 (CH_3^{tBu}), 41.64 (CH_2^{Gly}), 52.63, 52.65

($2CH_2^{Nasn}$), 53.25 (2-CH), 61.96 (6-CH_2), 68.24 (4-CH), 72.88 (3-CH), 73.52 (5-CH), 79.72 (1-CH), 82.81 (C^{tBu}), 169.41, 169.47, 170.80, 171.30, 171.54, 172.20, 172.31 ppm; IR (KBr): $\bar{\nu} = 3400$, 1847, 1749, 1662, 1524 cm^{-1}; HRMS (ESI): calcd. for $C_{24}H_{39}N_4O_{12}$ ($M + H^+$) 575.25590, found 575.25592.

tert-Butyl N-{2-Oxo-2-[(3,4,6-tri-O-acetyl-2-acetamido-2-deoxy-β-D-glucopyranosyl)-amino]ethyl}glycylalaninate (H-N*asn*(Ac_3-β-D-*Glc*N*Ac*)-*Ala*-O^t*Bu*, **7b**, $C_{25}H_{40}N_4O_{12}$)

HCl*H-*Ala*-O^t*Bu* (218 mg, 1.20 mmol) and **4b** (609 mg, 1.00 mmol) were reacted due to protocol 2. Reaction time: 2d. Purification by flash chromatography (*DCM*:*Me*OH = 15:1, $R_f = 0.35$). Yield 450 mg (76%), foam; $[\alpha]_D = -14^\circ\ cm^3\ g^{-1}\ dm^{-1}$ ($c = 1.3$, *DCM*); ^{1}H NMR (*DMSO*-d_6, 400 MHz, COSY): $\delta = 1.27$ (d, $J = 7.2$ Hz, CH_3^{Ala}), 1.40 (s, 9H, CH_3^{tBu}), 1.77 (s, N*Ac*), 1.92, 1.97, 2.00 (3s, 3O*Ac*), 3.07 (d, 1H, $J = 16.5$ Hz, CH_2^{Nasn}), 3.08 (s, CH_2^{Nasn}), 3.15 (d, 1H, $J = 16.5$ Hz, CH_2^{Nasn}), 3.86 (m, 5-H), 3.91–3.97 (m, 2-H, 6-H_a), 4.15–4.20 (m, 6-H_b, CH^{Ala}), 4.83 (dd, $J = 9.3$, 9.6 Hz, 4-H), 5.15 (dd, $J = 9.6$, 9.9 Hz, 1-H, 3-H), 7.99 (d, $J = 9.0$ Hz, NH*Ac*), 8.11 (d, $J = 7.2$ Hz, NH^{Ala}), 8.45 (d, $J = 9.0$ Hz, 1-NH) ppm; ^{13}C NMR (*DMSO*-d_6, 100 MHz, HMQC): $\delta = 17.03$ (CH_3^{Ala}), 20.29, 20.32, 20.42 (3O*Ac*), 22.42 (NH*Ac*), 27.52 (CH_3^{tBu}), 47.93 (CH^{Ala}), 51.43, 51.55 ($2CH_2^{Nasn}$), 51.94 (2-CH), 61.76 (6-CH_2), 68.47 (4-CH), 72.12 (5-CH), 72.73 (3-CH), 78.07 (1-CH), 80.36 (C^{tBu}), 169.22, 169.42, 169.93 (2C), 170.48, 171.56, 171.73 ppm; IR (KBr): $\bar{\nu} = 3600$–3300, 1745, 1665, 1534 cm^{-1}; HRMS (ESI): calcd. for $C_{25}H_{41}N_4O_{12}$ ($M + H^+$) 589.27155, found 589.27140.

tert-Butyl N-{2-Oxo-2-[(3,4,6-tri-O-acetyl-2-acetamido-2-deoxy-β-D-glucopyranosyl)-amino]ethyl}glycylsarcosinate (H-N*asn*(Ac_3-β-D-*Glc*N*Ac*)-N*ala*-O^t*Bu*, **5b**/**2**, $C_{25}H_{40}N_4O_{12}$)

HCl*H-*Sar*-O^t*Bu* (191 mg, 1.05 mmol) and **4b** (536 mg, 0.88 mmol) were reacted due to protocol 2. Reaction time: 4d. Purification by flash chromatography (*DCM*:*Me*OH = 15:1, $R_f = 0.21$). Yield 235 mg (45%), foam; $[\alpha]_D = +1^\circ\ cm^3\ g^{-1}\ dm^{-1}$ ($c = 2.3$, *DCM*); ^{1}H NMR ($CDCl_3$, 200 MHz, 300 K, COSY): rotational isomers, ratio: 3:1; $\delta = 1.45$ (s, $CH_3^{tBu}{}_{maj}$), 1.46 (s, $CH_3^{tBu}{}_{min}$), 1.90 (s, NH*Ac*), 2.02, 2.03, 2.07 (3s, 3O*Ac*), 2.96 (s, $NCH_3{}_{min}$), 2.97 (s, $NCH_3{}_{maj}$), 3.15–3.56 (m, $2CH_2^{Nasn}$), 3.77 (m, 5-H), 3.86–4.27 (m, CH_2^{Nala}, 6-H_2, 2-H), 5.07–5.21 (m, 1,3,4-H), 6.14 (d, $J = 9.3$ Hz, NH*Ac*), 8.13 (d, $J = 9.6$ Hz, 1-NH $_{min}$), 8.17 (d, $J = 9.6$ Hz, 1-NH $_{maj}$) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz, 300 K, HETCOR): $\delta = 20.73$, 20.82, 20.88 (3O*Ac*), 23.24 (NH*Ac*), 28.18 (CH_3^{tBu}), 35.19 ($CH_3^{Nala}{}_{min}$), 35.24 ($CH_3^{Nala}{}_{maj}$), 50.40 (CH_2^{Nala}, CH_2^{Nasn}), 52.73 (CH_2^{Nasn}), 53.39 (2-CH), 61.99 (6-CH_2), 68.17 (4-CH), 73.13 (3-CH), 73.75 (5-CH), 79.34 (1-CH), 82.09 (C^{tBu}), 168.21, 169.44, 170.80, 170.99, 171.05, 171.33, 171.38, 171.47, 172.73, 172.81 ppm; IR (KBr): $\bar{\nu} = 3600$–3300, 1745, 1662, 1522 cm^{-1}; HRMS (ESI): calcd. for $C_{25}H_{41}N_4O_{12}$ ($M + H^+$) 589.27155, found 589.27144.

tert-Butyl N-Trifluoroacetyl-N-benzylglycyl-N-{2-oxo-2-[(3,4,6-tri-O-acetyl-2-acetamido-2-deoxy-β-D-glucopyranosyl)amino]ethyl}glycylsarcosinate (*TFA*-N*phe*-N*asn*(Ac_3-β-D-*Glc*-N*Ac*)-N*ala*-O^t*Bu*, **6b**, $C_{36}H_{48}F_3N_5O_{14}$)

TFA-N*phe*-OH (52 mg, 0.20 mmol) and **5b**/**2** (100 mg, 0.17 mmol) were reacted due to protocol 3. Purification by flash chromatography (*DCM*:*Me*OH = 10:1, $R_f = 0.32$). Yield 78 mg (55%), colorless solid; purity >95% (HPLC); mp 171–173°C; $[\alpha]_D = -4^\circ\ cm^3\ g^{-1}\ dm^{-1}$ ($c = 1.6$, *DCM*); ^{19}F NMR ($CDCl_3$, 282 MHz, 300 K): 2 complex signal groups, ratio: 1:4; $\delta = 8.68$ (s), 9.50 (s), 9.54 (s), 9.61 (s) ppm; IR (KBr): $\bar{\nu} = 1745$, 1668, 1541 cm^{-1}; HRMS (ESI): calcd. for $C_{36}H_{49}F_3N_5O_{14}$ ($M + H^+$) 854.30421, found 854.30332; MS (FAB): $m/z = 854.3$ $[M + Na]^+$, 832.3 $[M + H]^+$, 776.3

$[M\text{-}C_4H_8 + H]^+$, 687.2 $[M\text{-}(Sar\text{-}O^tBu)]^+$, 486.1 $[M\text{-}(Ac_3\text{-}Glc\text{NA}c\text{-NH})]^+$, 430.0 $[M\text{-}(Ac_3\text{-}Glc\text{NA}c\text{-NH)-}C_4H_8)]^+$, 330.0 $[Ac_3\text{-}Glc\text{NA}c]^+$.

N-(2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl)-2-[5-oxo-2,2-bis(trifluoromethyl)-1,3-oxazolidin-3-yl]acetamide (**4c**, $C_{21}H_{24}F_6N_2O_{12}$)

Compound **3** (4.79 g, 16.0 mmol) and Ac_4-β-D-Gal-NH_2 (5.56 g, 16.0 mmol) were reacted due to protocol 1. Purification by flash chromatography (ethyl acetate:petrolether = 1:1, $R_f = 0.38$). Yield 7.63 g (78%), foam; $[\alpha]_D = +13°\ cm^3\ g^{-1}\ dm^{-1}$ ($c = 2.3$, *DCM*); ^{1}H NMR ($CDCl_3$, 300 MHz, COSY): $\delta = 1.99$, 2.03, 2.05, 2.17 (4s, 4O*Ac*), 3.64 (d, 1H, $J = 16.8$ Hz, CH_2^{Nasn}), 3.70 (d, 1H, $J = 16.8$ Hz, CH_2^{Nasn}), 3.76 (s, CH_2^{Nasn}), 4.03–4.12 (m, 6-H_2, 5-H), 5.05 (dd, $J = 9.6$, 9.9 Hz, 2-H), 5.13 (dd, $J = 3.3$, 10.2 Hz, 3-H), 5.19 (dd, $J = 9.0$, 9.3 Hz, 1-H), 5.41 (d, $J = 3.3$ Hz, 4-H), 7.10 (d, $J = 9.0$ Hz, 1-NH) ppm; ^{19}F NMR ($CDCl_3$, 282 MHz): $\delta = 1.49$ (m, 3F), 1.56 (m, 3F) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz, HETCOR): $\delta = 20.86$, 20.90, 20.96, 20.99 (4O*Ac*), 49.71, 51.66 ($2CH_2^{Nasn}$), 61.40 (6-CH_2), 67.47 (4-CH), 68.76 (2-CH), 71.06 (3-CH), 72.95 (5-CH), 78.87 (1-CH), 90.16 (sept, $J = 33$ Hz), 121.27 (q, $J = 291$ Hz), 121.34 (q, $J = 291$ Hz, CF_3), 166.15, 167.64, 170.14, 170.42, 170.76, 171.56 ppm; IR (KBr): $\bar{\nu} = 1850$, 1752, 1707, 1523 cm^{-1}; MS (FAB): $m/z = 611.2$ $[M + H]^+$.

tert-Butyl N-{2-Oxo-2-[(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)amino]ethyl}glycyl-glycinate (H-N*asn*(Ac_4-β-D-Gal)-*Gly*-O^t*Bu*, **5c**/**1**, $C_{24}H_{37}N_3O_{13}$)

HCl*H-*Gly*-O^t*Bu* (330 mg, 1.97 mmol) and **4c** (1000 mg, 1.64 mmol) were reacted due to protocol 2. Reaction time: 18 h. Purification by flash chromatography (CH_2Cl_2:*Me*OH = 20:1, $R_f = 0.29$). Yield 696 mg (74%), colorless foam; $[\alpha]_D = +13°\ cm^3\ g^{-1}\ dm^{-1}$ ($c = 1.2$, *DCM*); ^{1}H NMR ($CDCl_3$, 300 MHz, COSY): $\delta = 1.46$ (s, 9H, CH_3^{tBu}), 1.97, 2.02, 2.09, 2.13 (4s, 4O*Ac*), 3.26 (d, 1H, $J = 16.7$ Hz, CH_2^{Nasn}), 3.30 (s, 2H, CH_2^{Nasn}), 3.35 (d, 1H, $J = 16.7$ Hz, CH_2^{Nasn}), 3.96 (d, $J = 5.7$ Hz, CH_2^{Gly}), 3.98–4.11 (m, 5-H, 6-H_2), 5.06–5.17 (m, 2,3-H), 5.22 (dd, $J = 9.0$, 9.3 Hz, 1-H), 5.42 (d, $J = 2.3$ Hz, 4-H), 7.15 (br.t, $J = 5.7$ Hz, NH^{Gly}), 7.63 (d, $J = 9.0$ Hz, 1-NH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz, HETCOR): $\delta = 20.65$, 20.70, 20.78, 20.90 (4O*Ac*), 28.15 (CH_3^{tBu}), 41.72 (CH_2^{Gly}), 52.30, 52.40 ($2CH_2^{Nasn}$), 61.28 (6-CH_2), 67.27 (4-CH), 68.70 (2-CH), 70.85 (3-CH), 72.51 (5-CH), 78.35 (1-CH), 82.49 (C^{tBu}), 169.29, 169.85, 170.13, 170.54, 170.99, 171.58, 171.66 ppm; IR (KBr): $\bar{\nu} = 3600$–3300, 1747, 1662, 1535 cm^{-1}; HRMS (ESI): calcd. for $C_{24}H_{38}N_3O_{13}$ ($M + H^+$) 576.23991, found 576.23935.

tert-Butyl N-{2-Oxo-2-[(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)amino]ethyl}glycyl-leucinate (H-N*asn*(Ac_4-β-D-Gal)-*Leu*-O^t*Bu*, **7c**, $C_{28}H_{45}N_3O_{13}$)

HCl*H-*Leu*-O^t*Bu* (440 mg, 1.97 mmol) and **4c** (1000 mg, 1.64 mmol) were reacted due to protocol 2. Reaction time: 2 d. Purification by flash chromatography (*DCM*:*Me*OH = 23:1, $R_f = 0.30$). Yield 710 mg (68%), foam; $[\alpha]_D = +12°\ cm^3\ g^{-1}\ dm^{-1}$ ($c = 1.0$, *DCM*); ^{1}H NMR ($CDCl_3$, 300 MHz, COSY): $\delta = 0.96$ (d, $J = 6.0$ Hz, CH_3^{Leu}), 0.97 (d, $J = 6.3$ Hz, CH_3^{Leu}), 1.48 (s, 9H, CH_3^{tBu}), 1.57–1.68 (m, β-CH_2^{Leu}, γ-CH^{Leu}), 2.01, 2.05, 2.08, 2.16 (4s, 4O*Ac*), 3.26 (d, 1H, $J = 15.9$ Hz, CH_2^{Nasn}), 3.32 (s, 2H, CH_2^{Nasn}), 3.33 (d, 1H, $J = 15.9$ Hz, CH_2^{Nasn}), 4.04–4.14 (m, 6-H_2, 5-H), 4.55 (m, α-CH^{Leu}), 5.10–5.15 (m, 2,3-H), 5.25 (dd, $J = 9.0$, 9.3 Hz, 1-H), 5.45 (d, $J = 2.1$ Hz, 4-H), 6.85 (d, $J = 8.4$ Hz, NH^{Leu}), 7.63 (d, $J = 9.0$ Hz, 1-NH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz, APT, HETCOR): $\delta = 20.65$, 20.70, 20.79, 20.87 (4O*Ac*), 22.01 (CH_3^{Leu}), 22.98 (CH_3^{Leu}), 25.12 (γ-CH^{Leu}), 28.09 (CH_3^{tBu}), 41.55 (β-CH_2^{Leu}), 51.30 (α-CH^{Leu}), 52.21, 52.29 ($2CH_2^{Nasn}$), 61.29 (6-CH_2), 67.31 (4-CH), 68.52 (2-CH), 70.92 (3-CH), 72.56 (5-CH), 78.39 (1-CH), 82.19 (C^{tBu}), 169.88, 170.12, 170.42, 170.58, 171.47, 171.74, 172.44 ppm; IR (KBr): $\bar{\nu} = 3500$–3300, 1747, 1660, 1531 cm^{-1}; HRMS (ESI): calcd. for $C_{28}H_{46}N_3O_{13}$ ($M + H^+$) 632.30251, found 632.30422.

tert-Butyl N-{2-Oxo-2-[(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)amino]ethyl}glycyl-N-isobutylglycinate (H-N*asn*(*Ac*$_4$-β-D-*Gal*)-N*leu*-O^t*Bu*, **5c**/**2**, $C_{28}H_{45}N_3O_{13}$)

H-N*leu*-O^t*Bu* (504 mg, 2.69 mmol) and **4c** (1.37 g, 2.24 mmol) were reacted in ethyl acetate (10 cm^3) due to protocol 2. Reaction time: 4 d. Purification by flash chromatography (gradient elution ethyl acetate:petrolether = 3:1 → 6:1, $R_f = 0.25$). Yield 690 mg (49%), foam; $[\alpha]_D = +15°$ cm^3 g^{-1} dm^{-1} ($c = 2.5$, *DCM*); ^{1}H NMR ($CDCl_3$, 400 MHz, 300 K, COSY): rotational isomers, ratio: 1.9:1; $\delta = 0.90$ (d, $J = 6.6$ Hz, $CH_3^{Nleu}{}_{min}$), 0.93 (d, $J = 6.4$ Hz, $CH_3^{Nleu}{}_{min}$), 0.94 (d, $J = 6.6$ Hz, $CH_3^{Nleu}{}_{maj}$), 0.95 (d, $J = 6.4$ Hz, $CH_3^{Nleu}{}_{maj}$), 1.47 (s, $CH_3^{tBu}{}_{maj}$), 1.48 (s, $CH_3^{tBu}{}_{min}$), 1.82–1.90 (m, CH^{iBu}), 1.99–2.17 (several s, O*Ac*), 3.04 (d, $J = 7.5$ Hz, $CH_2^{iBu}{}_{maj}$), 3.20–3.38 (m, $CH_2^{iBu}{}_{min}$, $2CH_2^{Nasn}{}_{min}$, $CH_2^{Nasn}{}_{maj}$), 3.40 (d, 1H, $J = 16.3$ Hz, $CH_2^{Nasn}{}_{maj}$), 3.50 (d, 1H, $J = 16.3$ Hz, $CH_2^{Nasn}{}_{maj}$), 3.81 (d, 1H, $J = 18.5$ Hz, $CH_2^{Nleu}{}_{min}$), 3.89 (d, 1H, $J = 18.5$ Hz, $CH_2^{Nleu}{}_{min}$), 3.96 (s, $CH_2^{Nleu}{}_{maj}$), 4.01–4.15 (m, 5-H, 6-H_2), 5.12 (dd, $J = 2.8$, 10.0 Hz, 3-H), 5.17 (dd, $J = 10.0$, 9.3 Hz, 2-H), 5.25 (dd, $J = 9.3$, 9.6 Hz, 1-H $_{min}$), 5.26 (dd, $J = 9.3$, 9.6 Hz, 1-H $_{maj}$), 5.44 (d, $J = 2.8$ Hz, 4-H), 8.08 (d, $J = 9.6$ Hz, 1-NH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, 300 K, HMQC): $\delta = 20.10$ ($CH_3^{Nleu}{}_{maj}$), 20.13 ($CH_3^{Nleu}{}_{maj}$), 20.20 ($2CH_3^{Nleu}{}_{min}$), 20.61, 20.67, 20.73, 20.81 (4O*Ac*), 28.07 ($CH_3^{tBu}{}_{min}$), 28.14 ($CH_3^{tBu}{}_{maj}$), 49.01 ($CH_2^{Nleu}{}_{maj}$), 50.18 ($CH_2^{Nleu}{}_{min}$), 50.49, 52.91 ($2CH_2^{Nasn}$), 55.33 (CH_2^{iBu}), 61.33 (6-CH_2), 67.26 (4-CH), 68.61 (2-CH), 71.12 (3-CH), 72.47 (5-CH), 78.10 (1-CH), 81.96 ($C^{tBu}{}_{maj}$), 82.01 ($C^{tBu}{}_{min}$), 168.10, 169.88, 170.15, 170.41, 170.51, 171.28, 172.36 ppm; IR (KBr): $\bar{\nu} = 3500$–3300, 1746, 1650 cm^{-1}; HRMS (ESI): calcd. for $C_{28}H_{46}N_3O_{13}$ ($M + H^+$) 632.30251, found 632.30340.

tert-Butyl N-Benzoylglycyl-N-{2-oxo-2-[(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-amino]ethyl}glycylleucinate (*Bz-Gly*-N*asn*(*Ac*$_4$-β-D-*Gal*)-*Leu*-O^t*Bu*, **8c**, $C_{37}H_{52}N_4O_{15}$)

Bz-Gly-OH (116 mg, 0.65 mmol) and **7c** (341 mg, 0.54 mmol) were reacted due to protocol 3. Purification by flash chromatography ($CHCl_3$:*Me*OH = 10:1, $R_f = 0.24$). Yield 269 mg (62%), colorless crystals; mp 107–108°C; $[\alpha]_D = -3°$ cm^3 g^{-1} dm^{-1} ($c = 2.0$, *DCM*); ^{1}H NMR ($CDCl_3$, 600 MHz, 300 K, COSY): rotational isomers, ratio: 3:1; $\delta = 0.90$–0.97 (m, CH_3^{Leu}), 1.46 (s, $CH_3^{tBu}{}_{maj}$), 1.47 (s, $CH_3^{tBu}{}_{min}$), 1.53–1.73 (m, β-CH_2^{Leu}, γ-CH^{Leu}), 1.92–2.13 (several s, O*Ac*), 3.82 (d, 1H, $J = 16.3$ Hz, Hz, $CH_2^{Nasn}{}_{maj}$), 3.99–4.35 (m, $CH_2^{Nasn}{}_{maj}$ (3H), $2CH_2^{Nasn}{}_{min}$, CH_2^{Gly}, 5-H, 6-H_2), 4.42 (m, α-$CH^{Leu}{}_{maj}$), 4.51 (m, α-$CH^{Leu}{}_{min}$), 5.12 (dd, $J = 3.0$, 10.1 Hz, 3-H), 5.16 (dd, $J = 9.0$, 10.1 Hz, 2-H), 5.26 (dd, $J = 9.0$, 10.1 Hz, 1-H $_{maj}$), 5.30 (dd, $J = 9.0$, 10.1 Hz, 1-H $_{min}$), 5.42 (d, $J = 3.0$ Hz, 4-H $_{min}$), 5.43 (d, $J = 3.0$ Hz, 4-H $_{maj}$), 6.86 (d, $J = 7.2$ Hz, $NH^{Leu}{}_{min}$), 7.26 (partially covered by the chloroform signal, $NH^{Gly}{}_{min}$), 7.38 (br.t, $J = 4.8$ Hz, $NH^{Gly}{}_{maj}$), 7.41–7.44 (m, H^{meta}), 7.49–7.52 (m, H^{para}), 7.60 (d, $J = 7.2$ Hz, $NH^{Leu}{}_{maj}$), 7.84 (d, $J = 7.3$, $H^{ortho}{}_{min}$), 7.86 (d, $J = 7.3$ Hz, $H^{ortho}{}_{maj}$), 8.28 (d, $J = 9.0$ Hz, 1-NH $_{maj}$), 9.08 (d, $J = 9.0$ Hz, 1-NH $_{min}$) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz, 300 K, HMQC): $\delta = 20.6$–21.0 (O*Ac*), 22.02 ($CH_3^{Leu}{}_{maj}$), 22.15 ($CH_3^{Leu}{}_{min}$), 22.74 ($CH_3^{Leu}{}_{maj}$), 22.82 ($CH_3^{Leu}{}_{min}$), 24.87 (γ-$CH^{Leu}{}_{min}$), 25.12 (γ-$CH^{Leu}{}_{maj}$), 28.08 (CH_3^{tBu}), 41.13 (β-$CH_2^{Leu}{}_{maj}$), 41.60 (β-$CH_2^{Leu}{}_{min}$), 41.65 ($CH_2^{Gly}{}_{min}$), 41.73 ($CH_2^{Gly}{}_{maj}$), 51.87 (α-$CH^{Leu}{}_{min}$), 52.13 (α-$CH^{Leu}{}_{maj}$), 52.72 ($CH_2^{Nasn}{}_{maj}$), 52.87 ($CH_2^{Nasn}{}_{min}$), 54.05 ($CH_2^{Nasn}{}_{maj+min}$), 61.22 (6-CH_2), 67.18 (4-CH), 68.46 (2-CH $_{maj}$), 68.81 (2-CH $_{min}$), 71.18 (3-CH $_{maj}$), 71.33 (3-CH $_{min}$), 72.49 (5-CH $_{maj}$), 72.66 (5-CH $_{min}$), 78.48 (1-CH $_{maj}$), 78.72 (1-CH $_{min}$), 82.27 ($C^{tBu}{}_{maj+min}$), 127.25, 128.67, 131.92, 133.62 ($_{min}$), 133.72 ($_{maj}$), 167.4–171.9 ppm; IR (KBr): $\bar{\nu} = 3600$–3300, 1753, 1654, 1536 cm^{-1}; MS (FAB): $m/z = 793.3$ $[M + H]^+$, 737.3 $[M\text{-}C_4H_8 + H]^+$, 606.3 [M-*Leu*-O*tBu*]$^+$, 576.2 [M-(*Bz-Gly*)-(C_4H_8) + 2H]$^+$, 446.1 [M-(*Ac*$_4$-*Gal*-NH)]$^+$, 390.3 [M-(*Ac*$_4$-*Gal*-NH)-(C_4H_8)]$^+$, 331.0 [*Ac*$_4$-*Gal*]$^+$.

N-[2,3,6-Tri-O-acetyl-4-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-β-D-glucopyranosyl]-2-[5-oxo-2,2-bis(trifluoromethyl)-1,3-oxazolidin-3-yl]acetamide (**4d**, $C_{33}H_{40}F_6N_2O_{20}$)

Compound **3** (740 mg, 2.47 mmol) and *Ac*$_4$-β-D-*Glc*(1 → 4)-*Ac*$_3$-β-D-*Glc*-*NH*$_2$ (1.57 g, 2.47 mmol) were reacted due to protocol 1. Purification by flash chromatography (ethyl acetate:petroleum

ether = 2:1, $R_f = 0.39$). Yield 1.82 g (82%), foam; $[\alpha]_D = +8°$ cm^3 g^{-1} dm^{-1} ($c = 2.0$, *DCM*); ^{1}H NMR ($CDCl_3$, 400 MHz, COSY): $\delta = 1.98$, 2.01 (2s, 2O*Ac*), 2.03 (s, 3O*Ac*), 2.09, 2.12 (2s, 2O*Ac*), 3.62–3.72 (m, $2CH_2^{Nasn}$, 5-H, 5′-H), 3.77 (dd, $J = 9.0$, 9.0 Hz, 4-H), 4.05 (dd, $J = 1.8$, 12.4 Hz, 6′-H_a), 4.12 (dd, $J = 4.1$, 12.1 Hz, 6-H_a), 4.36 (dd, $J = 4.5$, 12.1 Hz, 6′-H_b), 4.49 (dd, $J = 1.0$, 12.1 Hz, 6-H_b), 4.51 (d, $J = 8.0$ Hz, 1′-H), 4.84 (dd, $J = 9.6$, 9.6 Hz, 2-H), 4.92 (dd, $J = 9.0$, 8.2 Hz, 2′-H), 5.06 (dd, $J = 9.5$, 9.7 Hz, 4′-H), 5.14 (dd, $J = 9.6$, 9.3 Hz, 1-H, 3′-H), 5.30 (dd, $J = 9.1$, 9.4 Hz, 3-H), 6.96 (d, $J = 9.0$ Hz, 1-NH) ppm; ^{19}F NMR ($CDCl_3$, 282 MHz): $\delta = 0.21$ (m, 3F), 0.40 (m, 3F) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz, HETCOR): $\delta = 20.45$ (2O*Ac*), 20.50 (3O*Ac*), 20.63, 20.79 (2O*Ac*), 49.29, 51.26 ($2CH_2^{Nasn}$), 61.28, 61.68 (6,6′-CH_2), 67.89 (4′-CH), 70.85 (2-CH), 71.57 (2′-CH), 71.99, 72.00 (5′,3-CH), 72.88 (3′-CH), 74.74, 76.10 (4,5-CH), 78.09 (1-CH), 89.72 (sept, $J = 33$ Hz), 100.65 (1′-CH), 120.84 (q, $J = 291$ Hz), 120.94 (q, $J = 289$ Hz), 165.62, 167.20, 168.97, 169.29, 169.38, 170.18 (2C), 170.45, 171.10; IR (KBr): $\bar{\nu} = 1848$, 1755, 1521 cm^{-1}; MS (FAB): $m/z = 899.5$ $[M + H]^+$.

tert-Butyl N-{2-Oxo-2-[(2,3,6-tri-O-acetyl-4-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-β-D-glucopyranosyl)amino]ethyl}glycylglycinate
(H-N*asn*(*Ac*$_4$-β-*D*-*Glc*-(1 → 4)-*Ac*$_3$-β-*D*-*Glc*)-*Gly*-O^t*Bu*, **5d**/**1**, $C_{36}H_{53}N_3O_{21}$)

HCl*H-*Gly*-O^t*Bu* (66 mg, 0.40 mmol) and **4d** (297 mg, 0.33 mmol) were reacted due to protocol 2. Reaction time: 18 h. Purification by flash chromatography (*DCM*:*Me*OH = 10:1, $R_f = 0.28$). Yield 258 mg (90%), foam; $[\alpha]_D = -7°$ cm^3 g^{-1} dm^{-1} ($c = 1.3$, *DCM*); ^{1}H NMR ($CDCl_3$, 400 MHz, COSY): $\delta = 1.49$ (s, 9H, CH_3^{tBu}), 1.99, 2.01 (2s, 2O*Ac*), 2.03 (s, 3O*Ac*), 2.09, 2.12 (2s, 2O*Ac*), 3.29–3.34 (m, $2CH_2^{Nasn}$), 3.66 (ddd, $J = 2.3$, 4.4, 9.8 Hz, 5′-H), 3.74–3.78 (m, 4,5-H), 3.97 (d, $J = 5.6$ Hz, CH_2^{Gly}), 4.05 (dd, $J = 2.3$, 12.5 Hz, 6′-H_a), 4.13 (dd, $J = 3.4$, 11.8 Hz, 6-H_a), 4.36 (dd, $J = 4.4$, 12.5 Hz, 6′-H_b), 4.48 (dd, $J = 1.2$, 11.8 Hz, 6-H_b), 4.51 (d, $J = 8.0$ Hz, 1′-H), 4.88 (dd, $J = 9.6$, 9.6 Hz, 2-H), 4.92 (dd, $J = 9.3$, 8.0 Hz, 2′-H), 5.07 (dd, $J = 9.6$, 9.6 Hz, 4′-H), 5.15 (dd, $J = 9.3$, 9.3 Hz, 3′-H), 5.19 (dd, $J = 9.3$, 9.3 Hz, 1-H), 5.29 (dd, $J = 9.3$, 9.3 Hz, 3-H), 7.14 (br.t, $J = 5.6$ Hz, NH^{Gly}), 7.55 (d, $J = 9.3$ Hz, *1-NH*) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, HMQC): $\delta = 20.59$ (2O*Ac*), 20.62 (2O*Ac*), 20.73, 20.77, 20.93 (3O*Ac*), 28.13 (CH_3^{tBu}), 41.78 (CH_2^{Gly}), 51.99, 52.19 ($2CH_2^{Nasn}$), 61.78, 61.84 (6,6′-CH_2), 68.00 (4′-CH), 71.15 (2-CH), 71.68 (2′-CH), 72.11, 72.24 (3,5′-CH), 72.98 (3′-CH), 74.73, 76.15 (4,5-CH), 78.00 (1-CH), 82.78 (C^{tBu}), 100.65 (1′-CH), 169.25, 169.41, 169.48, 169.67, 170.40, 170.65, 170.68, 171.30, 171.63, 171.91 ppm; IR (KBr): $\bar{\nu} = 3600$–3300, 1749, 1655, 1540 cm^{-1}; HRMS (ESI): calcd. for $C_{36}H_{54}N_3O_{21}$ $(M + H^+)$ 864.32443, found 864.32419.

tert-Butyl N-{2-Oxo-2-[(2,3,6-tri-O-acetyl-4-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-β-D-glucopyranosyl)amino]ethyl}glycylprolinate
(H-N*asn*(*Ac*$_4$-β-*D*-*Glc*-(1 → 4)-*Ac*$_3$-β-*D*-*Glc*)-*Pro*-O^t*Bu*, **7d**, $C_{39}H_{57}N_3O_{21}$)

HCl*H-*Pro*-O^t*Bu* (247 mg, 1.19 mmol) and **4d** (890 mg, 0.99 mmol) were reacted due to protocol 2. Reaction time: 3 d. Purification by flash chromatography (*DCM*:*Me*OH = 15:1, $R_f = 0.29$). Yield 600 mg (67%), foam; $[\alpha]_D = -27°$ cm^3 g^{-1} dm^{-1} ($c = 1.9$, *DCM*); ^{1}H NMR ($CDCl_3$, 300 MHz, 300 K, COSY): rotational isomers, ratio: 5:1, δ (major rotamer) = 1.44 (s, 9H, CH_3^{tBu}), 1.96, 1.99, 2.00 (3s, 3O*Ac*), 2.01 (s, 2O*Ac*), 2.08, 2.11 (2s, 2O*Ac*), 1.85–2.20 (m, β,γ-CH_2^{Pro}), 3.24 (d, 1H, $J = 17.1$ Hz, CH_2^{Nasn}), 3.32 (s, 2H, CH_2^{Nasn}), 3.33 (d, 1H, $J = 17.1$ Hz, CH_2^{Nasn}), 3.36–3.51 (m, δ-CH_2^{Pro}), 3.64 (m, 5′-H), 3.71–3.78 (m, 4,5-H), 4.01–4.11 (m, 6′,6-H_a), 4.32–4.44 (m, 6′,6-H_b, α-CH^{Pro}), 4.49 (d, $J = 8.1$ Hz, 1′-H), 4.84–4.93 (m, 2,2′-H), 5.04 (dd, $J = 9.3$, 9.6 Hz, 4′-H), 5.13 (dd, $J = 9.0$, 9.3 Hz, 3′-H), 5.20 (dd, $J = 9.3$, 9.6 Hz, 1-H), 5.25 (dd, $J = 9.3$, 9.6 Hz, 3-H), 7.83 (d, $J = 9.6$ Hz, 1-NH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz, 300 K): δ (major rotamer) = 20.5–21.0 (7O*Ac*), 24.64 (γ-CH_2^{Pro}), 28.05 (CH_3^{tBu}), 29.07 (β-CH_2^{Pro}), 45.96 (δ-CH_2^{Pro}), 50.97, 52.40 ($2CH_2^{Nasn}$), 59.82 (α-CH^{Pro}), 61.78, 61.93 (6,6′-CH), 68.02, 71.10, 71.69, 72.11, 72.47, 73.05, 74.69, 76.22 (2,3,4,5,2′,3′,4′,5′-CH), 77.77 (1-CH), 81.95 (C^{tBu}), 100.69 (1′-CH), 169.14, 169.17, 169.44, 169.62,

170.35, 170.43, 170.63, 170.71, 171.43, 172.41 ppm; IR (KBr): $\bar{\nu} = 3600$–3300, 1751, 1645 cm^{-1}; HRMS (ESI): calcd. for $C_{39}H_{58}N_3O_{21}$ $(M + H^+)$ 904.35573, found 904.35375.

tert-Butyl N-Trifluoroacetyl-N-isobutylglycyl-N-{2-oxo-2-[(2,3,6-tri-O-acetyl-4-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-β-D-glucopyranosyl)amino]ethyl}glycylprolinate
(*TFA*-N*leu*-N*asn*(*Ac*$_4$-*β-D-Glc*-(1 → 4)-*Ac*$_3$-*β-D-Glc*)-*Pro*-O^t*Bu*,
8d, $C_{47}H_{67}F_3N_4O_{23}$)

TFA-N*leu*-OH (45 mg, 0.20 mmol) and **7d** (150 mg, 0.17 mmol) were reacted due to protocol 3. Purification by chromatography (ethyl acetate:$CHCl_3$:*Me*OH = 5:5:1, $R_f = 0.30$). Yield 80 mg (42%), colorless solid; purity > 95% (HPLC); mp 121–122°C; $[\alpha]_D = -30^\circ$ $cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.2$, *DCM*); ^{19}F NMR ($CDCl_3$, 282 MHz, 300 K): 2 complex signal groups, ratio: 1:4; $\delta = 4.16$ (s), 4.20 (s), 4.24 (s), 4.33 (s), 5.57 (s), 5.65 (s), 5.73 (s), 5.81 (s) ppm; HRMS (ESI): calcd. for $C_{47}H_{68}F_3N_4O_{23}$ $(M + H^+)$ 1113.42210, found 1113.42221; MS (FAB): $m/z = 1135.4$ $[M + Na]^+$, 1113.4 $[M + H]^+$, 1079.3 $[M\text{-}C_4H_8 + Na]^+$, 942.4 [M-(*Pro*-O^t*Bu*)]$^+$, 478.3 [M-(*Ac*$_7$-Cellobiosyl-NH)]$^+$, 422.2 [M-(*Ac*$_7$-Cellobiosyl-NH)-C_4H_8]$^+$, 331.2 [*Ac*$_4$-*Glc*]$^+$.

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