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Note

Iodine-mediated glycosylation *en route* to mucin-related glyco-aminoacids and glycopeptides☆

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Abstract—The use of iodine–DDQ as a promoter for glycosylation of Fmoc-Ser-OBn and Fmoc-Thr-OBn with phenylseleno 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-D-galactopyranoside in toluene–dioxane gave 49% and 73% yields, respectively, of the corresponding α-glycosides as the sole glycoside products. Reductive acetylation of the azide groups and cleavage of the benzyl esters by hydrogenolysis gave building blocks that were used in solid-phase synthesis to prepare triglycosylated tetrapeptides $(Ac_3GalNAc\text{-}\alpha\text{-}Ser)_3$-Gly and $(Ac_3GalNAc\text{-}\alpha\text{-}Thr)_3$-Gly in 27% and 49% overall yield, respectively.

Keywords: Aminoacid; Glycosylation; Iodine–DDQ; Phenyl selenoglycoside; Glycopeptide; Mucin

In connection with our interests in the development of carbohydrate microarrays,[2] and extending our interest in aminoacid glycosylation[3] and glycopeptide synthesis,[4] we had a need to prepare small mucin-related O-linked glycopeptides. Such compounds are of interest in relation to cancer diagnostics and vaccines; the literature covering the role of chemical synthesis in this area has been reviewed recently.[5] Herein we describe the development of practical stereospecific syntheses of *N*-(fluoren-9-ylmethoxycarbonyl)-*O*-(2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-α-D-galactopyranosyl)-L-serine and *N*-(fluoren-9-ylmethoxycarbonyl)-*O*-(2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-α-D-galactopyranosyl)-L-threonine, and the solid-phase synthesis of short glycopeptides derived therefrom.

Aminoacid glycosylation with phenylseleno 3,4,6-tri-O-acetyl-2-azido-2-deoxy-α-D-galactopyranoside (**1**): The ease with which phenylseleno 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-D-galactopyranoside (**1**)[6] can be prepared from galactose (via azidophenylselenation of tri-*O*-acetyl-D-galactal) makes it an attractive choice as a glycosyl donor[7] for the synthesis of α-GalNAc-containing glycosides.[8] In addition, the facile activation of thioglycosides[1,9] and selenoglycosides[1,10] with iodine and related agents prompted us to investigate their use in the current context. Mindful that glycosyl iodide formation might result from selenoglycoside activation,[1] we also considered the use of iodine in combination with DDQ,[11] which appears to overcome this issue, enabling solvent-mediated glycosylation stereocontrol in the context of acetonitrile-controlled β-glycosylation.[1] In the current study we required α-stereocontrol; hence we investigated the use of non-participating dichloromethane and participating toluene–dioxane.[12] In the latter case, the reaction is thought to proceed via a *O*-β-glycosyl oxonium ion derived from dioxane (as opposed to an

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Table 1. Impact of solvent and promoter on glycosylation yield and stereoselectivity

Acceptor	Solvent	Promoter: iodine[a]		Promoter: iodine + DDQ[a]	
		Time (h)	Yield (α:β)	Time (h)	Yield (α:β)
Methanol	CH_2Cl_2	2	52% (4:1)	2	68% (1.3:1)
Methanol	Toluene–dioxane 1:3	24	18% (5:1)	24	66% (15:1)
Cyclohexanol	CH_2Cl_2	5	85% (4:1)	23	49% (2.7:1)
Cyclohexanol	Toluene–dioxane 1:3	31	29% (18:1)	24	61% (20:1)
Fmoc-Ser-OMe	CH_2Cl_2	24	44% (10:1)	22	45% (8:1)
Fmoc-Ser-OMe	Toluene–dioxane 1:3	27	31% (7:1)	24	53% (7.8:1)
Fmoc-Thr-OMe	CH_2Cl_2	3	61% (6.7:1)	7	75% (8.4:1)
Fmoc-Thr-OMe	Toluene–dioxane 1:3	26	25% (α only)	26	34% (α only)
Fmoc-Ser-OBn	Toluene–dioxane 1:3			24	49% (α only)[b]
Fmoc-Thr-OBn	Toluene–dioxane 1:3			24	73% (α only)[b]

[a] Analytical reactions were carried out with donor (100 mg, 0.2 mmol) in solvent (1 mL) at room temperature with iodine (1.5 mol equiv) ± DDQ (1.5 mol equiv) and with either 4 mol equiv acceptor (methanol, cyclohexanol) or 1.5 mol equiv acceptor (aminoacid derivatives). The stereochemical outcome of the reactions was assessed by ^{1}H NMR spectroscopy.

[b] Preparative reactions performed on a 10 mmol scale.

α-glycosyl nitrilium ion when acetonitrile is used,[13]) with S_N2 displacement then giving the α-glycoside. In the initial studies, a series of alcohol acceptors of varying reactivity were investigated (Table 1).

Regardless of the acceptor, glycosylation reactions in toluene/dioxane were much slower but gave a better stereocontrol than in dichloromethane. Both the rate of the reaction and the α-stereoselectivity were enhanced by using iodine in combination with DDQ, rather than iodine alone.[‡] Intramolecular hydrogen bonding within the acceptor (side-chain oxygen to Fmoc-NH)[14] may contribute to the sluggishness of this series of glycosylation reactions. However, when the more potent promoter IBr[15] was employed, improved reactivity (46% yield in 3.5 h) was off-set by reduced stereocontrol (α:β, 1:1.4). It has been reported that the choice of aminoacid carboxyl protection can impact on reactivity and glycosylation yields,[16] but in the current study little difference was observed between the methyl and benzyl glycosides of Fmoc-Ser and Fmoc-Thr when compared. On a preparative scale (~10 mmol), respectable yields (49% and 73%, respectively) were obtained for the glycosylation of Fmoc-Ser-OBn and Fmoc-Thr-OBn building blocks, giving glyco-aminoacids (**2**) and (**3**). The lack of formation of the undesired β-anomer makes for straightforward purification of the known α-linked products;[17] the predominant by-product appears to be hemi-acetal in both cases, as judged by TLC analysis.

Generation of partially protected GalNAc-α-O-Ser/Thr: Reductive acetylation[18] of azides (**4**) and (**5**) gave acetamides (**6**) and (**7**), respectively, in good yield. Subsequent (careful) hydrogenation[3a,17] cleaved the benzyl esters, giving compounds (**8**) and (**9**), which are suitable for direct use in solid-phase peptide synthesis (Scheme 1).

Glycopeptide synthesis: Protocols employed for solid-phase glycopeptide synthesis were as described previously.[4,19] Briefly, commercial Fmoc-Gly-Wang resin, which enables acid-catalysed cleaved of the final glycopeptide, was deprotected with piperidine and either GalNAc-serine building block (**8**) or GalNAc-threonine building block (**9**) was coupled with the aid of TBTU in the presence of HOBt. Three rounds of such deprotection/coupling, followed by removal of the N-terminal Fmoc group and acid-mediated cleavage of the peptide from the resin, gave triglycosylated tetrapeptides (**10**) and (**11**) (Scheme 2), the variants of which have been prepared previously by solution-phase synthesis.[17,23]

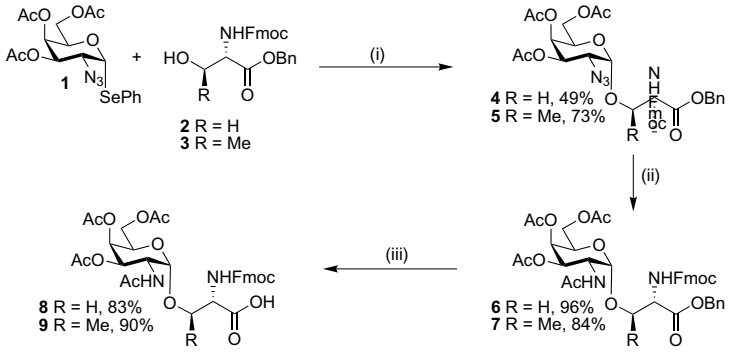
In summary, we have developed a short and convenient gram-scale procedure for the glycosylation of serine and threonine derivatives *en route* to α-GalNAc-Ser/Thr building blocks for mucin glycopeptide synthesis. Our approach is based on a readily accessible selenoglycoside donor and employs a combination of iodine and DDQ in toluene/dioxane to achieve essentially exclusive α-stereoselectivity in the glycosylation step.

1. Experimental

1.1. Materials and general methods

The reactions were carried out in dry solvents using septa and syringes for the addition of reagents. Dry CH_2Cl_2 and toluene were prepared by distillation from CaH_2;

[‡] With phenylselenide donor (**1**), DDQ alone did not give significant glycosylation of methanol in toluene/dioxane, whereas in acetonitrile glycosylation occurred with reasonable efficiency and stereocontrol (41% yield in 19 h; α:β, 1:10).



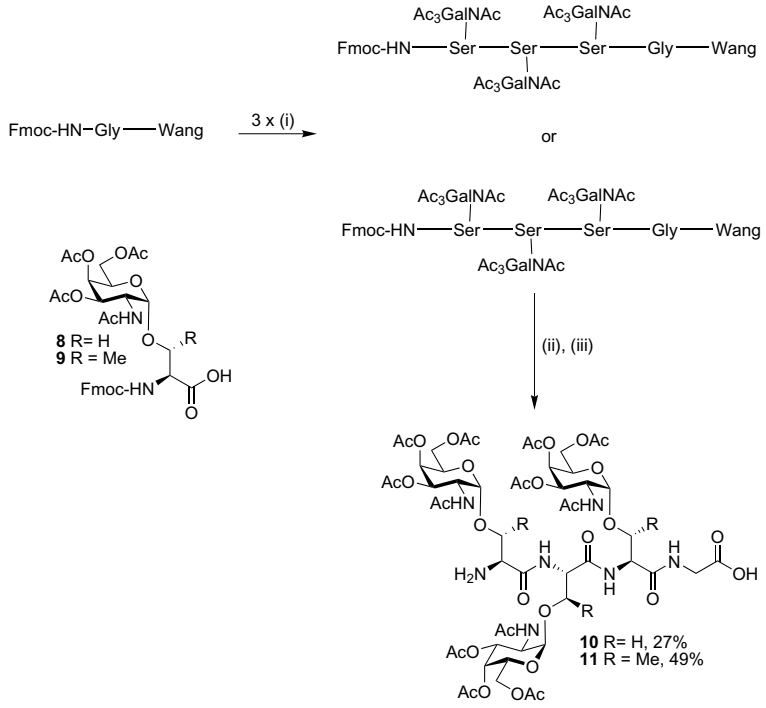
Scheme 1. Reagents and conditions: (i) I_2, DDQ, toluene–dioxane, 1:3; (ii) Zn, $CuSO_4$, THF–Ac_2O–AcOH; (iii) Pd–C, H_2, MeOH, AcOH.

dioxane was distilled from sodium-benzophenone. TLC was performed on pre-coated aluminium plates (Silica Gel 60 F_{254}, Merck). Spots were visualised by exposure to UV light or by immersion in 5% ethanolic H_2SO_4 followed by heating to 150 °C. The solutions of reaction products were dried over $MgSO_4$ and the solvents were evaporated under reduced pressure at 25–40 °C. Column chromatography was performed on silica gel (40–70 μm, BDH-Merck). Optical rotations were measured at 25 °C using a Perkin–Elmer 141 polarimeter. ^1H and ^{13}C NMR spectra were recorded at 21 °C with a Varian Unity Plus spectrometer at 400 and 100 MHz, respectively, using TMS as an internal standard. Accurate electrospray ionisation mass spectra (HR ESI-MS) were obtained using positive ionisation mode on a Finnigan MAT 900 XLT mass spectrometer. FAB mass spectra were recorded on a Finnigan MAT INCOS 50 mass spectrometer. The following known compounds were products of the experiments reported herein; all gave analytical data consistent with the literature: phenyl 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-1-seleno-α-D-galactopyranoside (**1**);[5] *N*-(fluoren-9-ylmethoxycarbonyl)-L-serine benzyl ester (**2**);[20] *N*-(fluoren-9-ylmethoxycarbonyl)-L-threonine benzyl ester (**3**);[21] *N*-(fluoren-9-ylmethoxycarbonyl)-*O*-(2-acetamido-2-de oxy-3,4,6-tri-*O*-acetyl-α-D-galactopyranosyl)-L-serine benzyl ester (**6**);[17] *N*-(fluoren-9-ylmethoxycarbonyl)-*O*-(2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-α-D-galactopyranosyl)-L-threonine benzyl ester (**7**);[17,22] *N*-(fluoren-9-ylmethoxycarbonyl)-*O*-(2-acetamido-2-deoxy-3,4,6-tri-*O*- acetyl-α-D-galactopyranosyl)-L-serine (**8**);[22] *N*-(fluoren-9-ylmethoxycarbonyl)-*O*-(2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-α-D-galactopyranosyl)-L-threonine (**9**).[22]

1.2. Typical procedure for preparative scale iodine–DDQ promoted glycosylation

1.2.1. *N*-(Fluoren-9-ylmethoxycarbonyl)-*O*-(3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-D-galactopyranosyl)-L-serine benzyl ester (4). Iodine (810 mg, 3.20 mmol) and DDQ (730 mg, 3.20 mmol) were added to a mixture of phenyl 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-1-seleno-α-D-galactopyranoside (**1**) (1.0 g, 2.13 mmol), *N*-(fluoren-9-ylmethoxycarbonyl)-L-serine benzyl ester (**2**) (1.07 g, 2.55 mmol) and dry toluene–1,4-dioxane mixture (1:3, v/v, 10 mL). The reaction was monitored by TLC (CH_2Cl_2–acetone 97:3, v/v). Aqueous sodium thiosulfate solution (15% w/v, 50 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was washed with aqueous sodium thiosulfate solution (15% w/v, 10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. Column chromatography (hexane–EtOAc 3:2, v/v) gave *N*-(fluoren-9-yl-methoxycarbonyl)-*O*-(3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-D-galactopyranosyl)-L-serine benzyl ester (**4**) (765 mg, 49%) as a white foam. $[\alpha]_D^{21}$ +81.9 (*c* 1, $CHCl_3$); $R_f = 0.54$ (CH_2Cl_2–acetone 97:3, v/v); ^1H NMR (500 MHz; Me_2SO): δ 1.89, 2.00, 2.11 (3 × s, 9H, 3 × CH_3–C=O), 3.72 (dd, 1H, $J_{1,2} = 3.4$, $J_{2,3} = 11.2$ Hz , H-2), 3.82–4.07 (m, 4H, H-6, H-6′, CH_2–CH–N), 4.21–4.39 (m, 4H, H-5, H-9^d, Fmoc CH_2), 4.55 (m, 1H, C*H*–N), 5.12 (d, 1H, H-1), 5.17 (m, 2H, CH_2-Ar), 5.31 (d, 1H, $J_{3,4} = 2.9$ Hz, H-4), 5.35 (dd, 1H, H-3), 7.27–7.45 (m, 9H, H-2^d, H-3^d, H-6^d, H-7^d, ArH from Bn group), 7.72 (t, 2H, $J = 8.3$ Hz, H-1^d, H-8^d), 7.88 (d, 2H, $J = 7.4$ Hz, H-4^d, H-5^d), 8.12 (d, 1H, $J = 8.3$ Hz, N*H*); ^{13}C NMR (75.4 MHz; Me_2SO) δ 20.3 (3 × *C*H$_3$–C=O), 46.6 (C-9^d), 54.1 (*C*H–N), 56.8 (C-2), 61.5 (C-6), 66.0, 66.4, 67.4, 67.7 (C-3, C-4, C-5, *C*H$_2$-Ar, Fmoc *C*H$_2$, Ser *C*H$_2$), 97.6 (C-1), 120.2, 125.3, 127.1, 127.7, 127.8, 128.1, 128.4, 128.9 (13 × Ar*C*, tertiary), 135.8 (Ar*C*, quaternary from Bn group), 140.8, 143.8 (4 × Ar*C*, quaternary from Fmoc group), 156.3 (HN–*C*=O from Fmoc group), 169.5, 169.9, 170.1 (3 × CH_3–*C* =O, BnO–*C*=O); ES-MS: *m*/*z* 753 (40%, $[M+Na]^+$), 731 (10, $[M+H]^+$, calcd for $C_{37}H_{39}O_{12}$ 731.2564, found 731.2577). ^1H NMR data are in accord with the literature.[17]

1.2.2. *N*-(Fluoren-9-ylmethoxycarbonyl)-*O*-(3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-D-galactopyranosyl)-L-threonine benzyl ester (5). The title compound prepared as described for the corresponding serine derivative was



Scheme 2. Reagents and conditions: (i) (1) 20% piperidine in DMF; (2) HBTU, HOBt, DIPEA, **8** or **9**, DMF; (ii) 20% piperidine in DMF; (iii) TFA–H_2O, 95:5.

obtained as a white foam (73% yield) $[\alpha]_D^{21}$ +42.1 (*c* 1, $CHCl_3$); $R_f = 0.53$ (CH_2Cl_2–acetone 97:3, v/v); ^1H NMR (300 MHz Me_2SO): δ 1.25 (d, 3H, $J = 6.0$ Hz, Thr CH_3), 1.95, 1.99, 2.11 (3 × s, 9H, 3 × CH_3–C=O), 3.81 (dd, 1H, $J_{1,2} = 3.3$, $J_{2,3} = 11.5$ Hz, H-2), 3.94–4.18 (m, 4H, H-6, H-6′, CH–C–N), 4.20–4.41 (m, 4H, H-5, H-9[d], Fmoc CH_2), 4.50 (m, 1H, CH–N), 5.03–5.39 (m, 5H, H-1, H-3, H-4, CH_2-Ar), 7.24–7.48 (m, 9H, H-2[d], H-3[d], H-6[d], H-7[d], ArH from Bn group), 7.73 (m, 2H, H-1[d], H-8[d]), 7.89 (d, 2H, $J = 7.4$ Hz, H-4[d], H-5[d]), 7.97 (d, 1H, $J = 8.3$ Hz, NH); ^{13}C NMR (75.4 MHz Me_2SO): δ 17.5 (Thr CH_3), 20.4 (3 × CH_3–C=O), 46.6 (C-9[d]), 57.4 (CH–N), 59.1 (C-2), 61.7 (C-6), 65.9, 66.4, 67.5, 68.3 (C-3, C-4, C-5, CH_2-Ar, Fmoc CH_2, C H–CH–N), 98.5 (C-1), 120.1, 125.3, 127.1, 127.7, 127.9, 128.1, 128.4 (13 × ArC, tertiary), 135.8 (ArC, quaternary from Bn group), 140.8, 143.8 (4 × ArC, quaternary from Fmoc group), 156.3 (HN–C=O from Fmoc group), 169.5, 169.9, 170.1 (3 × CH_3–C=O, BnO–C=O); EI-MS: (NOBA matrix) *m*/*z* 767 (25%, $[M+Na]^+$), 745 (35, $[M+H]^+$); ES-MS *m*/*z* 745 ($[M+H]^+$, calcd for $C_{38}H_{41}N_4O_{12}$ 745.2721, found 745.2722). NMR data are in accord with the literature.[17]

1.3. General procedures for solid-phase synthesis[4,19]

Fmoc-Gly-Wang resin (loading 0.69 mmol/g) was swelled in DMF for 30 min. The Fmoc group was removed by treating the resin with piperidine (20% in DMF) for 2 × 15 min. The resin was washed with DMF (×5) and CH_2Cl_2 (×5). Couplings were carried out by dissolving glycosyl-aminoacid, HOBt and HBTU in a small amount of DMF and by adding DIPEA. The mixture was added to the resin and the reaction mixture was left to stand. After 18 h the resin was washed successively with DMF (×5) and CH_2Cl_2 (×5). The Kaiser/ninhydrin test[19] was performed and the completeness of the coupling step was confirmed by cleavage with trifluoroacetic acid (TFA) on a small scale and ES-MS analysis of the resulting peptide. The Fmoc removal and coupling procedures were repeated three times. Cleavage was accomplished by adding TFA solution (TFA–water, 95:5, v/v) and agitating gently with N_2. After 3 h (30 min for small scale cleavage) the resin was filtered over cotton wool and TFA was evaporated in vacuo. The resulting crude peptide was carefully washed with cold ether (×2). The product was purified by reversed-phase HPLC (Phenomenex 5 μm Luna C18 column 250 mm × 10 mm, at 1.5 mL/min, eluting with a gradient from 95% H_2O–5% MeCN–plus 0.1% TFA to 5% H_2O–95% MeCN–plus 0.1% TFA over 7 column columns. UV detection at 220 nm and 280 nm).

1.3.1. *O*-(2-Acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-α-D-galactopyranosyl)-L-serinyl-*O*-(2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-α-D-galactopyranosyl)-L-serinyl-*O*-(2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-α-D-galactopyranosyl)-L-serinyl-L-glycine (20).

The synthesis was carried out using FmocGlyWang (145 mg, 0.10 mmol), *N*-(fluoren-9-ylmethoxycarbonyl)-*O*-(2-acetamido-2-deoxy-3,4,6-

tri-*O*-acetyl-α-D-galactopyranosyl)-L-serine **11** (163 mg, 0.25 mmol, 2.5 M equiv), DIPEA (75 μL, 0.5 mmol, 5 M equiv), HOBt (34 mg, 0.25 mmol, 2.5 M equiv) and HBTU (93 mg, 0.25 mmol, 2.45 M equiv). The glycopeptide (37 mg, 27%) was obtained after three rounds of coupling procedures: deprotection with piperidine, cleavage with TFA and HPLC purification. ^{1}H NMR (400 MHz D_2O): δ 1.80–2.04 (m, 36H, 9 × C*H*$_3$–CO–O, 3 × C*H*$_3$–CO–N), 3.67–4.08 (m, 14H, Gly CH_2, 3 × Ser CH_2, 6 × H-6), 4.10–4.33 (m, 7H, 3 × H-2, 3 × H-5, 1 × C*H*-N), 4.50–4.63 (m, 2H, 2 × C*H*–N, partly underneath HDO signal), 4.85–4.92 (m, 3H, 3 × H-1), 5.01–5.11 (m, 3H, 3 × H-3), 5.24–5.28 (m, 3H, 3 × H-4); ES-MS: $C_{53}H_{77}N_7O_{32}$ requires 1324 *m*/*z* 1346 (20%, $[M+Na]^+$), 1324 (100, M^+), 1282 (70, $[M-Ac]^+$), 1240 (40, $[M-2Ac]^+$).

1.3.2. *O*-(2-Acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-α-D-galactopyranosyl)-L-threoninyl-*O*-(2-acetamido-2-deoxy-3,4,6-tri-*O* -acetyl-α-D-galactopyranosyl)-L-threoninyl-*O*-(2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-α-D-galactopyranosyl)-L-threoninyl-L-glycine (21). The threonine-containing peptide was prepared as described above for the serine analogue. The glycopeptide (67 mg, 49%) was obtained after three rounds of coupling procedures: deprotection with piperidine, TFA cleavage and HPLC purification. ^{1}H NMR (400 MHz; D_2O): δ 1.19 (m, 6H, 2 × C*H*$_3$–CH), 1.33 (d, 3H, $J = 5.7$ Hz, C*H*$_3$–CH), 1.80–2.04 (m, 36H, 9 × C*H*$_3$–CO–O, 3 × C*H*$_3$–CO–N), 3.61 (d, 1H, $J = 18.1$ Hz, 1 × Gly CH_2), 3.94–4.42 (m, 18H, 3 × H-2, 3 × H-5, 6 × H-6, 1 × Gly CH_2, 3 × CH$_3$–C*H*, 2 × C*H*–N), 4.67 (m, 1H, C*H*–N, underneath HDO signal), 4.93 (d, 1H, $J = 3.8$ Hz, H-1), 4.96–5.13 (m, 5H, 2 × H-1, 3 × H-3), 5.21–5.31 (m, 3H, 3 × H-4); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 18.3, 18.5 (3 × C*H*$_3$–CH), 20.2, 20.3, 20.5 (9 × C*H*$_3$–CO–O), 22.1, 22.3 (3 × C *H*$_3$–CO–N), 40.9 (Gly CH_2), 47.5, 47.8 (3 × C-2), 57.4 (3 × *C*H–N), 62.7 (3 × C-6), 67.0, 67.2 (2 × C-5), 68.4 (3 × C-4), 68.9, 69.4 (3 × C-3, C-5), 75.4, 77.8, 78.1 (3 × CH$_3$– *C*H), 99.4 (3 × C-1), 171.4, 171.7 (3 × CH$_3$–*C*O–N), 173.0, 173.2, 173.4, 173.7, 174.4 (9 × CH$_3$–*C* O–O); FAB-MS: (NOBA matrix) $C_{56}H_{83}N_7O_{32}$ requires 1365 *m*/*z* 1366 (15%, $[M+H]^+$), 1365 (25, M^+).

Acknowledgements

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