Straightforward Synthesis of 2-Acetamido-2-deoxy-β-D-glucopyranosyl Esters under Microwave Conditions

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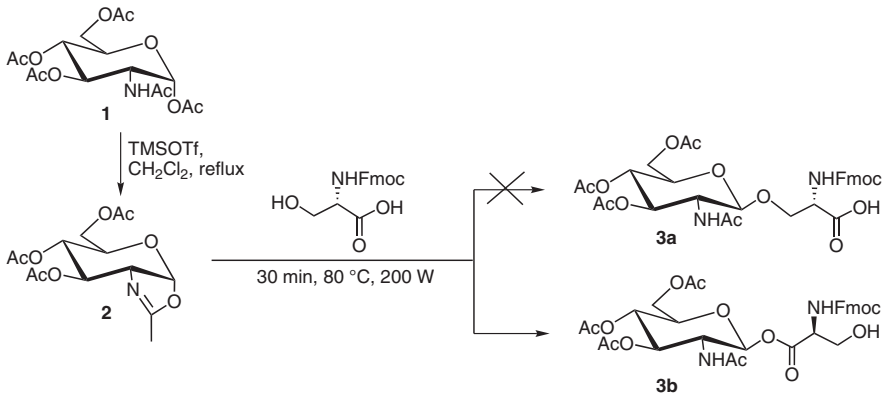
Abstract: A straightforward synthesis of 2-acetamido-2-deoxy-β-D-glucopyranosyl esters from unprotected GlcNAc oxazoline has been achieved under catalyst-free, microwave conditions.

Key words: glycosyl esters, glycomimetics, GlcNAc oxazoline, microwaves, catalyst-free

Carbohydrates, either linked to proteins, lipids, or as polysaccharides are ubiquitous features of biomolecules and are involved in many important functions such as cell communication, protein stability, and activity or immunity.[1] Glycoconjugates are typically referred to as *O*- or *N*-glycosides, depending on the nature of the heteroatom connecting the carbohydrate moiety to the aglycon. Glycosyl esters, in which the sugar head is linked to the aglycon via an ester linkage, represent a less common family of glycosides and are encountered in natural products such as the ellagitannin[2] and phyllanthostatin[3] families of antitumor agents. The potent immunoadjuvant QS21-A, isolated from *Quillajia saponaria*, is a complex saponin glycoside in which a tetrasaccharide is attached at the C-28 carboxylate of the triterpene moiety.[4] The ovine submaxillary gland mucoprotein contains 2-acetamido-2-deoxy-D-galactosyl (GalNAc) moieties bound by an ester linkage to the aspartic and glutamic acid side chains.[5] A β-1,3-glucan glutamate ester has recently been identified in the fungal cell wall Pir protein of *Saccharomyces cerevisiae*.[6] Acyl glucuronides are metabolite products of mycophenolic acid[7] and nonsteroidal anti-inflammatory drugs such as ibuprofen, naproxen, and diclofenac.[8]

Synthesis of glycosyl esters has been achieved using coupling reagents such as DCC,[9] imidazole,[10] by Mitsunobu reaction,[3,11] Yamaguchi anhydride derivative,[12] or with assistance of a C-2 participating neighboring group.[13] A glycosyl trichloroacetimidate has been used to synthesize ester-linked glycosyl dopamine derivatives as potential antiparkinsonian prodrugs.[14] Besides, glycosyl esters are sometimes encountered as side products of glycosylation reactions.[15] However, the key issue of the glycosyl ester formation is the anomeric selectivity, often controlled by the rate of mutarotation in a given solvent.[11,16] For example, Binkley et al.[17] have studied the synthesis of penta-*O*-galloyl-D-glucopyranose as a model reaction and investigated conditions leading to high anomeric selectivity.

As part of our ongoing effort towards the synthesis of glycopeptides and the design of glycoarrays,[18] an unexpected outcome in the synthesis of *N*-acetyl-D-glucosaminyl serine prompted us to investigate the reactivity of GlcNAc oxazoline with carboxylic acids under microwave conditions. The oxazoline of D-GlcNAc is a well-known glycosyl donor and has been extensively used for the preparation of glycoconjugates in combination with numerous Lewis acids.[19]However, when per-O-acetylated GlcNAc oxazoline **2** (prepared by refluxing the per-O-acetylated 2-acetamido-2-deoxy-α-D-glucopyranose **1** in dry dichloromethane in the presence of a stoichiometric



Scheme 1

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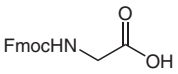
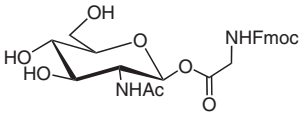
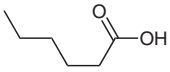
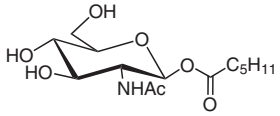
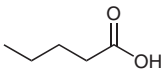
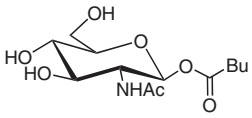
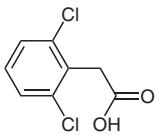
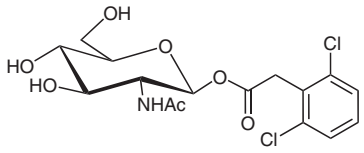
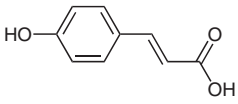
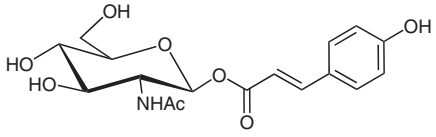
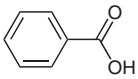
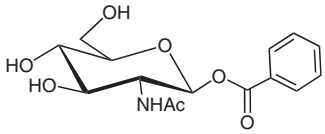
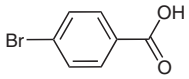
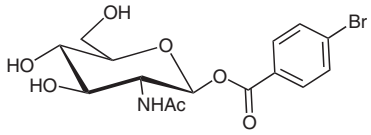
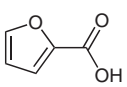
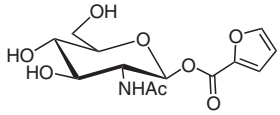
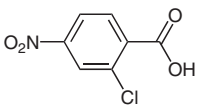
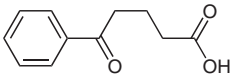
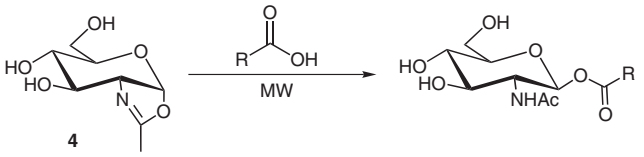
amount of TMSOTf)[20] was reacted with *N*-Fmoc serine under microwave conditions and in the absence of any Lewis acid (Scheme 1), careful examination of the NMR spectrum of the product **3b** obtained revealed an ester linkage between the GlcNAc and the serine in the β-configuration instead of the O-glycosylated amino acid **3a**.[21]

A possible explanation for this reaction is the protonation of the oxazoline nitrogen first, favoring attack of the anomeric center by the nucleophilic carboxylate[15d] from the β-face, thereby accounting for the complete stereoselectivity of this transformation. However, the use of acetyl protecting groups prevented any deprotection of the sugar moiety without cleaving the anomeric ester linkage.

Table 1 Reaction of GlcNAc-oxazoline with Carboxylic Acids

Entry	Carboxylic acid	Product and yield
1		 **5** 63%
2		 **6** 55%
3		 **7** 60%
4		 **8** 40%
5		 **9** 45%
6		 **10** 60%
7		 **11** 50%
8		 **12** 55%
9		starting material
10		–



Scheme 2

Therefore, we turned our attention towards the use of unprotected sugar oxazoline **4** (Scheme 2), reasoning that under these conditions no glycosylation of the hydroxyl groups would take place as found out with the serine amino acid. De-O-acetylation of **2** was readily achieved upon treatment with a catalytic amount of sodium in dry methanol to give **4**. Initial experiments were conducted using **4** and *N*-Fmoc glycine. Under optimized conditions [30 min, 80 °C, 200 W in acetonitrile–*N*,*N*-dimethylformamide (10:1)], the corresponding ester **5** was obtained in 63% isolated yield (Table 1, entry 1). A variety of carboxylic acids were then screened to evaluate the scope of this reaction (Table 1, entries 2–10). All compounds were characterized by NMR spectroscopy after column chromatography purification, and a complete β stereoselectivity was obtained in all cases. Reaction with aliphatic acids afforded the corresponding products **6** and **7** in 55% and 60% yield, respectively (entries 2 and 3). The reaction also proved compatible with carboxylic acids carrying various functionalities, such as 2,6-dichlorophenylacetic acid (entry 4, 40% **8**) and coumaric acid (entry 5, 45% **9**). In the case of aromatic carboxylic acids, benzoic acid, 4-bromobenzoic acid and furoic acid (entries 6–8) reacted with **4** to afford the desired esters **10** (60%), **11** (50%), and **12** (55%), respectively. However, 2-chloro-4-nitrobenzoic acid (entry 9) failed to react with **4**, and only starting materials were recovered. This result is probably due to the low nucleophilicity of the carboxylate caused by the electron-withdrawing 4-NO_2 group. Finally, reaction with 4-benzoylbutyric acid (entry 10) only lead to decomposition products.

In conclusion, we have described the preparation of novel glycosyl esters of 2-acetamido-2-deoxy-β-D-glucopyranose in fairly good yields under catalyst-free, microwave conditions. This straightforward method proved compatible with a range of diverse functionalized carboxylic acids, while avoiding the need for any coupling reagent and overcoming the issue of anomeric selectivity. Noteworthy, the reaction can be performed directly from unprotected oxazoline. Such method will be valuable for attachment of sugar moiety onto biomolecules and the synthesis of novel glycomimetics and glycopeptide analogues.

Experimental Procedures and Spectroscopic Data

2-Methyl-(3,4,6-tri-*O*-acetyl-1,2-dideoxy-α-D-glucopyrano)-[2,1-*d*]-2-oxazoline (2)[20]

1,2,3,4,6-Penta-*O*-acetyl-α-D-glucopyranose (**1**, 1.5 g, 3.85 mmol) was refluxed for 16 h in dry CH_2Cl_2 (20 mL) under argon in the presence of TMSOTf (850 μL, 4.62 mmol, 1.20 equiv). The reaction mixture was then quenched with Et_3N, evaporated under reduced pressure, and the residue was purified by flash chromatography over silica gel (eluent: CH_2Cl_2–MeOH = 98:2) to yield 1.03 g (3.13 mmol, 81%) of **2** as a brown oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.98 (d, 1 H, $J_{1,2}$ = 7.2 Hz, H-1), 5.27 (m, 1 H, H-3), 4.93 (d, 1 H, $J_{4,3} = J_{4,5}$ = 9.0 Hz, H-4), 4.18 (m, 3 H, H-2, H-6a, 6b), 3.61 (m, 1 H, H-5), 2.12, 2.11, 2.10, 2.09 (4 s, 12 H, 4 CH_3).

2-Methyl-(1,2-dideoxy-α-D-glucopyrano)-[2,1-*d*]-2-oxazoline (4)

To a solution of compound **2** in anhyd MeOH (2 mL) was added a catalytic amount of sodium. The reaction was stirred at r.t. for 2 h, then quenched with 1 M HCl. The solvent was removed under reduced pressure, and the crude product **4** was used without further purification.

^{1}H NMR (400 MHz, CD_3OD): δ = 5.99 (d, 1 H, $J_{1,2}$ = 7.2 Hz, H-1), 4.01 (m, 1 H, H-2), 3.87 (t, 1 H, $J_{2,3}$ = 3.6 Hz, H-3), 3.78–3.75 (dd, 1 H, $J_{6a,6b}$ = 12.4 Hz, $J_{6a,5}$ = 2.4 Hz, H-6a), 3.65–3.61 (dd, 1 H, $J_{6b,5}$ = 6.8 Hz, H-6b), 3.54–3.50 (m, 1 H, H-4), 3.35–3.31(ddd, 1 H, $J_{5,6a}$ = 2.4 Hz, $J_{5,6b}$ = 6.4 Hz, $J_{5,4}$ = 9.2 Hz, H-5), 2.02 (s, 3 H, CH_3).

Typical Procedure for the Synthesis of Glycosyl Ester

Oxazoline **4** (1 mmol) and carboxylic acid (1 mmol) were dispensed into a microwave tube and dissolved in a 3 mL mixture of MeCN–DMF (10:1). The tube was placed in a CEM Discover Microwave Synthesizer. The reaction mixture was heated at 80 °C with a ramping time of 5 min then stirring for 28 min (200 W, 16.6 bar). The crude product was concentrated in vacuo and purified by flash chromatography over silica gel eluted with EtOAc–MeOH.

***N*-(9-Fluorenylmethoxycarbonyl)-L-serine (2-acetamido-2-deoxy–β-D-glucopyranosyl) Ester (5)**

Eluent (EtOAc–MeOH = 8:2); yield 63%.

^{1}H NMR [400 MHz, $(CD_3)_2SO$]: δ = 7.78–7.77 (m, 2 H, H_{ar}), 7.71 (m, 2 H, H_{ar}), 7.41 (m, 2 H, H_{ar}), 7.34–7.32 (m, 2 H, H_{ar}), 5.49 (m, 1 H, H-1), 4.13 (m, 1 H, CH_{Fmoc}), 4.26–4.24 (m, 2 H, CH_{2Fmoc}), 3.79–3.57 (m, 4 H, H-2, H-6a, $CH_{2β}$), 3.48–3.45 (m, 1 H, H-6b), 3.37–3.35 (m, 1 H, H-3), 3.17–3.16 (m, 2 H, H-4, H-5), 1.89 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, CD_3SO): δ = 172.2, 169.1, 156.5 (2 C), 143.8 (2 C), 140.7 (2 C), 127.7 (2 C), 127.1 (2 C), 125.2 (2 C), 120.1 (2 C), 93.6, 78.1, 73.5, 69.9, 65.8, 60.5, 54.3, 46.6, 41.9, 22.9.

HRMS: *m/z* calcd for $C_{25}H_{28}N_2O_9$ $[M + H]^+$: 501.1873; found: 501.1879.

2-Acetamido-2-deoxy-1-*O*-hexanoyl-β-D-glucopyranose (6)

Eluent (EtOAc–MeOH = 9:1); yield 55%.

^{1}H NMR (400 MHz, CD_3OD): δ = 5.61–5.59 (d, 1 H, $J_{1,2}$ = 8.8 Hz, H-1), 3.87–3.82 (ta, 2 H, *J* = 9.6 Hz, H-2, H-6a), 3.71–3.67 (m, 1 H, H-6b), 3.52–3.48 (t,1 H, $J_{3,4} = J_{3,2}$ = 8.5 Hz, H-3), 3.38 (m, 2 H, H-4, H-5), 2.36–2.31 (m, 2 H, CH_2), 1.95 (s, 3 H, CH_3), 1.64–1.57 (qu, 2 H, *J* = 7.2 Hz, CH_2), 1.38–1.29 (m, 4 H, 2 CH_2), 0.92 (t, 3 H, *J* = 7.2 Hz, CH_3).

^{13}C NMR (100 MHz, CD_3OD): δ = 173.9, 173.6, 94.1, 78.8, 75.8, 71.6, 62.6, 56.3, 35.3, 32.3, 25.5, 23.5, 23.0, 14.4.

HRMS: *m/z* calcd for $C_{14}H_{25}NO_7$ $[M + Na]^+$: 342.1529; found: 342.1541.

2-Acetamido-2-deoxy-1-*O*-pentanoyl-β-D-glucopyranose (7)

Eluent (EtOAc–MeOH = 9:1); yield 60%.

^{1}H NMR (400 MHz, CD_3OD): δ = 5.61–5.59 (d, 1 H, $J_{1,2}$ = 8.8 Hz, H-1), 3.87–3.82 (m, 2 H, H-2, H-6a), 3.71–3.67 (dd, 1 H, $J_{6b,6a}$ = 12.4 Hz, $J_{6b,5}$ = 3.0 Hz, H-6b), 3.52–3.48 (m,1 H, H-3), 3.38

(m, 2 H, H-4, H-5), 2.25–2.23 (m, 2 H, CH_2), 1.95 (s, 3 H, CH_3), 1.64–1.57 (q, 2 H, J = 6.9 Hz, CH_2), 1.34–1.29 (sx, 2 H, J = 6.9 Hz, CH_2), 0.93–0.90 (t, 3 H, J = 6.2 Hz, CH_3).

^{13}C NMR (100 MHz, CD_3OD): δ = 173.8, 173.6, 94.2, 78.9, 75.7, 71.6, 62.4, 56.2, 34.8, 27.9, 23.2, 22.9, 14.1.

HRMS: *m/z* calcd for $C_{13}H_{23}NO_7$ [M + H]$^+$: 306.1553; found: 306.1549.

2-Acetamido-2-deoxy-1-*O*-(2,6-dichlorophenylacetyl)-β-D-glucopyranose (8)
Eluent (EtOAc–MeOH = 9:1); yield 40%.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.40–7.35 (t, 2 H, J = 9.5 Hz, H_{ar}), 7.29–7.26 (m, 1 H, H_{ar}), 5.67–5.64 (d, 1 H, $J_{1,2}$ = 11.0 Hz, H-1), 4.05–4.03 (d, 2 H, J = 8.0 Hz, CH_2), 3.88–3.80 (m, 2 H, H-2, H-6a), 3.73–3.68 (m, 1 H, H-6b), 3.55–3.47 (m, 1 H, H-3), 3.40–3.38 (m, 2 H, H-4, H-5), 1.94 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, CD_3OD): δ = 173.6, 169.7, 137.2 (2 C), 130.7, 129.3 (2 C), 129.1, 94.8, 79.1, 75.7, 71.6, 62.4, 56.2, 37.3, 23.0.

HRMS: *m/z* calcd for $C_{16}H_{19}Cl_2NO_7$ [M + Na]$^+$: 430.0436; found: 430.0444.

2-Acetamido-1-*O*-(*p*-coumaryl)-2-deoxy-β-D-glucopyranose (9)
Eluent (EtOAc–MeOH = 8:2); yield 45%.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.71 (d, 1 H, J = 15.6 Hz, H_{all}), 7.49 (d, 2 H, J = 8.7 Hz, H_{ar}), 6.83 (d, 2 H, J = 8.5 Hz, H_{ar}), 6.31 (d, 1 H, J = 15.6 Hz, H_{all}), 5.68 (d, 1 H, $J_{1,2}$ = 8.8 Hz, H-1), 4.00–3.95 (dd, 1 H, $J_{2,1}$ = 8.8 Hz, $J_{2,3}$ = 10.0 Hz, H-2), 3.91–3.87 (dd, 1 H, $J_{6a,6b}$ = 12.4 Hz, $J_{6a,5}$ = 1.6 Hz, H-6a), 3.75–3.71 (dd, 1 H, $J_{6b,6a}$ = 12.0 Hz, $J_{6b,5}$ = 4.8 Hz, H-6b), 3.58–3.54 (m, 1 H, H-3), 3.45–3.43 (m, 2 H, H-4, H-5), 1.96 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, CD_3OD): δ = 173.9, 167.5, 161.7, 148.5, 131.5 (2 C), 126.9, 116.9 (2 C), 114.1, 94.5, 78.9, 75.8, 71.5, 62.5, 56.3, 22.9.

HRMS: *m/z* calcd for $C_{17}H_{21}NO_8$ [M + Na]$^+$: 390.1165; found: 390.1147.

2-acetamido-1-*O*-benzoyl-2-deoxy-β-D-glucopyranose (10)
Eluent (EtOAc–MeOH = 9:1); yield 60%.

^{1}H NMR (400 MHz, CD_3OD): δ = 8.05–8.03 (d, 2 H, J = 8.0 Hz, H_{ar}), 7.63 (t, 1 H, J = 7.2 Hz, H_{ar}), 7.50–7.47 (t, 2 H, J = 7.2 Hz, H_{ar}), 5.76 (d, 1 H, $J_{1,2}$ = 8.8 Hz, H-1), 4.07 (t, 1 H, $J_{2,1}$ = 8.8 Hz, H-2), 3.89–3.86 (dd, 1 H, $J_{6a,6b}$ = 12.0 Hz, $J_{6a,5}$ < 1 Hz, H-6a), 3.70 (dd, 1 H, $J_{6b,6a}$ = 12.0 Hz, $J_{6b,}5$< 1.0 Hz, H-6b), 3.60–3.55 (m, 1 H, H-3), 3.46 (m, 2 H, H-4, H-5), 1.90 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, CD_3OD): δ = 173.3, 166.0, 134.4, 130.5, 130.0 (2 C), 129.3 (2 C), 94.6, 78.6, 75.1, 71.1, 62.0, 55.6, 22.7.

HRMS: *m/z* calcd for $C_{15}H_{19}NO_7$ [M + Na]$^+$: 348.1059; found: 348.1077.

2-Acetamido-1-*O*-(4-bromobenzoyl)-2-deoxy-β-D-glucopyranose (11)
Eluent (EtOAc–MeOH = 9:1); yield 50%.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.87–7.82 (d, 2 H, J = 8.8 Hz, H_{ar}), 7.61–7.55 (d, 2 H, J = 8.8 Hz, H_{ar}), 5.70 (d, 1 H, $J_{1,2}$ = 8.8 Hz, H-1), 4.00–3.95 (m, 1 H, H-2), 3.83–3.80 (m, 1 H, H-6a), 3.75–3.71 (m, 1 H, H-6b), 3.58–3.54 (m, 1 H, H-3), 3.43–3.40 (da, 2 H, J = 6.4 Hz, H-4, H-5), 1.96 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, CD_3OD): δ = 173.6, 167.0, 132.6 (2 C), 132.4 (2 C), 129.8, 127.2, 95.3, 79.0, 75.4, 71.6, 62.4, 56.0, 22.9.

HRMS: *m/z* calcd for $C_{15}H_{18}BrNO_7$ [M + H]$^+$: 404.0345; found: 404.0352.

2-Acetamido-2-deoxy-1-*O*-furoyl-β-D-glucopyranose (12)
Eluent (EtOAc–MeOH = 8:2). Yield: 55%.

^{1}H NMR (400 MHz, CD_3OD): δ = 8.18 (dd, 1 H, J = 0.8–1.6 Hz, H_{ar}), 7.60 (t, 1 H, J = 1.6 Hz, H_{ar}), 6.77 (dd, 1 H, J = 0.4–1.6 Hz, H_{ar}), 5.70 (d, 1 H, $J_{1,2}$ = 8.8 Hz, H-1), 3.99–3.94 (dd, 1 H, $J_{2,1}$ = 8.8 Hz, $J_{2,3}$ = 1.2 Hz, H-2), 3.88–3.85 (dd, 1 H, H-6a, $J_{6a,6b}$ = 12.0 Hz, $J_{6a,5}$ = 1.2 Hz, H-6a), 3.73–3.70 (m, 1 H, H-6b), 3.57–3.52 (m, 1 H, H-3), 3.44–3.43 (m, 2 H, H-4, H-5), 1.92 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, CD_3OD): δ = 173.8, 162.9, 150.5, 145.8, 119.8, 110.6, 94.7, 78.9, 75.5, 71.6, 62.4, 56.1, 22.9.

HRMS: *m/z* calcd for $C_{13}H_{17}NO_8$ [M + H]$^+$: 316.1035; found: 316.1039.

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