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ORIGINAL PAPER

I_2-mediated α-selective Ferrier glycosylation approach to synthesis of *O*-glycosyl amino acids

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I_2 is an effective promoter for the synthesis of 2,3-unsaturated glycosides via Ferrier glycosylation. This reaction was used in the present work for the synthesis of *O*-glycosylated Fmoc amino acid building blocks. This metal-free reaction afforded the desired products with good to excellent yields with good α-selectivity.
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Keywords: *O*-glycosides, Ferrier rearrangement, I_2, α-selectivity

Introduction

Glycoproteins, which have been reported as playing pivotal roles in processes as diverse as fertilisation, neuronal development, hormone activities, immune surveillance and inflammatory responses (Bertozzi & Kiessling, 2001; Dwek, 1996; Rudd et al., 2001; Talbot et al., 2003; Varki, 1993), are the key to understanding many complex biological processes. Hence, much effort has been devoted to developing facile methods for synthesising glycopeptides.

Currently, there are two major assembly strategies for synthesising *O*-glycopeptides: convergent assembly (Wang et al., 2000; Halkes et al., 2001; Schleyer et al., 1997) and building block assembly (St. Hilaire et al., 1998; Mitchell et al., 2001; van Ameijde et al., 2002). The latter method, which possesses many advantages, for example, glycosylated amino acid building blocks can be easily introduced into solid-phase syntheses through peptide chemistry, has been widely applied to the preparation of a wide variety of glycopeptides and even large glycopeptide libraries (Kunz, 1987; Kihlberg & Elofsson, 1997; Herzner et al., 2000). Accordingly, the preparation of glycosylated amino acid building blocks attracts ever-increasing interest.

The *O*-glycosidic bond in *O*-linked glycans is usually formed through glycosylation of the hydroxyl group of an appropriately protected serine (Ser) or threonine (Thr), using some standard glycosyl donors (Tsuda & Nishimura, 1996; Jensen et al., 1993). Although the α-glycosidic bonds are typically found in natural *O*-glycopeptides, the method of constructing this type of pattern represents a challenge to *O*-glycopeptide synthesis. A general method for preparing α-glycosyl amino acid building blocks for the synthesis of *O*-glycopeptides was reported by Kunz (1987) In this case, α-glycosyl amino acids were synthesised by the glycosylation reaction of per-*O*-acetylated-2-azido-2-deoxy-hexopyranosyl bromides (prepared in the first step by the azidonitration reaction of per-*O*-acetylated glycal using ceric ammonium nitrate) (Lemieux & Ratcliffe, 1979) and *N*-(9-fluorenylmethoxycarbonyl)-L-threonine *tert*-butyl ester (Fmoc-Thr-OtBu) promoted with $AgClO_4$/Ag_2CO_3. Subsequently, improved procedures have introduced various glycosyl donors for the preparation of *O*-glycopeptides with suitable promoters, such as trimethylsilyl trifluoromethanesulfonate (TMSOTf), phenyl sulfoxide/trifluoroacetic anhydride (Ph_2SO/Tf_2O), and Ag_2CO_3. All of these methods, however, suffer from low yields or long reaction times.

Glycals, viz. 1,2-unsaturated derivatives of pentoses and hexoses, are among the most versatile of chiral building blocks and have attracted considerable

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interest in carbohydrate chemistry (Lemieux & Ratcliffe, 1979). One of the most investigated and most exploited synthetic transformations for the initial step in glycal chemistry is the Ferrier rearrangement (Collins & Ferrier, 1995), which produces the 2,3-unsaturated *O*-glycosides. The 2,3-double bond in the pyran ring of these molecules can readily be modified by dihydroxylation, hydrogenation, epoxidation and aminohydroxylation to achieve structural complexity and diversity. Due to their potential use as chiral building blocks, 2,3-unsaturated-*O*-glycosides are suited to be the precursors of the *O*-glycosyl amino acids.

I_2 was recently used for the thioglycosidation of D-glycals with various thiols through Ferrier rearrangement by Subba Reddy et al. (2010). This inspired us to study its application in glycosylation reactions with certain amino acids. As a part of ongoing research into the synthesis of *O*-glycopeptides, a glycosylation method was developed using I_2 as the promoter (Fig. 1) to prepare *O*-glycosylated *N*-Fmoc amino acid (Fmoc denotes an amine-protecting group, 9-fluorenylmethoxycarbonyl) building blocks. An effective approach to accessing 2,3-unsaturated glycosyl amino acids with good α-selectivity is reported here.

Experimental

The starting glycals were prepared using known general method (Franz et al., 2002). All the other chemicals were commercially available as analytical-purity reagents from Merck (Germany) and used without further purification. TLC was performed on precoated silica gel HSGF254 plates (0.5 mm, Yantai, China). Flash column chromatography was performed on silica gel H (100–140 mesh, Yantai, China). Melting points (uncorrected) were determined using a Büchi B-540 melting points apparatus (Büchi, Switzerland). NMR spectra were recorded using a Bruker Avance 600 MHz spectrometer (Bruker, Germany). Optical rotations were determined at ambient temperature on a Perkin–Elmer 241 MC polarimeter with the sodium D line. ESI-MS spectra were obtained on an Agilent 1100 mass spectrometer (Agilent Technologies, USA).

General procedure for synthesis of glycosyl amino acids

I_2 (0.5–1.0 eq) was added to a stirred mixture of acetylated glycal (1.0 eq) and *N*-Fmoc amino acids (1.0 eq) in dry CH_2Cl_2 (10 mL) and the reaction mixture was stirred at ambient temperature (unless stated otherwise) for 0.5–1 h (monitored by TLC). The reaction proceeding in the mixture was quenched with $Na_2S_2O_3$ and the products extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4 and filtered through Celite in a sintered funnel. Evaporation of the solvent gave a crude oil that was purified on a silica gel column using petroleum ether/EtOAc (φ_r = 5 : 1) as eluent to afford the product. Thus, starting from 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-l-enitol (3,4,6-tri-*O*-acetyl-D-glucal, *Ia*) or 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*lyxo*-hex-l-enitol (3,4,6-tri-*O*-acetyl-D-galactal, *Ib*) or 3,4-di-*O*-acetyl-1,5-anhydro-2,6-dideoxy-D-*arabino*-hex-l-enitol (3,4-di-*O*-acetyl-D-rhamnal, *Ic*) or 3,4-di-*O*-acetyl-1,5-anhydro-2-deoxy-D-*threo*-pent-1-enitol (3,4-di-*O*-acetyl-D-xylal, *Id*) or 3,4-di-*O*-acetyl-1,5-anhydro-2-deoxy-D-*erythro*-pent-1-enitol (3,4-di-*O*-acetyl-D-arabinal, *Ie*) and *N*-(9-fluorenylmethoxycarbonyl)-L-serine benzyl ester (Fmoc-Ser-OBn), corresponding *O*-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*arabino*-hex-2-enopyranosyl)-*N*-(9-fluorenylmethoxycarbonyl)-L-serine benzyl ester (*IIa*) or *O*-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*lyxo*-hex-2-enopyranosyl)-*N*-(9-fluorenylmethoxycarbonyl)-L-serine benzyl ester (*IIb*) or *O*-(4-*O*-acetyl-2,3,6-trideoxy-α-D-*arabino*-hex-2-enopyranosyl)-*N*-(9-fluorenylmethoxycarbonyl)-L-serine benzyl ester (*IIc*) or *O*-(4-*O*-acetyl-2,3-dideoxy-α-D-*threo*-pent-2-enopyranosyl)-*N*-(9-fluorenylmethoxycarbonyl)-L-serine benzyl ester (*IId*) or *O*-(4-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-pent-2-enopyranosyl)-*N*-(9-fluorenylmethoxycarbonyl)-L-serine benzyl ester (*IIe*), respectively, were obtained. Analogously, starting from glycal *Ia* and *N*-(9-fluorenylmethoxycarbonyl)-L-serine (Fmoc-Ser-OH) or *N*-(9-fluorenylmethoxycarbonyl)-L-threonine benzyl ester (Fmoc-Thr-OBn) or *N*-(9-fluorenylmethoxycarbonyl)-L-tyrosine benzyl ester (Fmoc-Tyr-OBn), corresponding *O*-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*arabino*-hex-2-enopyranosyl)-*N*-(9-fluorenylmethoxycarbonyl)-L-serine (*IIf*) or *O*-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*arabino*-hex-2-enopyranosyl)-*N*-(9-fluorenylmethoxycarbonyl)-L-threonine benzyl ester (*IIg*) or *O*-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*arabino*-hex-2-enopyranosyl)-*N*-(9-fluorenylmethoxycarbonyl)-L-tyrosine benzyl ester (*IIh*), respectively, were prepared (see Fig. 1, Table 1).

Table 1. Characterisation data of newly prepared compounds

Compound	Formula	*M*r	$[\alpha]_D^a$/°	M.p./℃
IIa	$C_{35}H_{35}NO_{10}$	629.65	+27.4	48–50
IIb	$C_{35}H_{35}NO_{10}$	629.65	–94.7	57–59
IIc	$C_{33}H_{33}NO_8$	571.62	–35.5	119–124
IId	$C_{32}H_{31}NO_8$	557.59	+53.9	49–50
IIe	$C_{32}H_{31}NO_8$	557.59	–63.7	40–41.0
IIf	$C_{28}H_{29}NO_{10}$	539.53	+42.7	38–39.0
IIg	$C_{36}H_{37}NO_{10}$	643.24	+7.5	48–49
IIh	$C_{41}H_{39}NO_{10}$	705.28	+11.4	243–246

a) (c = 1.08, $CHCl_3$, T = 20 ℃).

Results and discussion

Initial studies were aimed at optimisation of the reaction conditions for the glycosylation reaction of

Table 2. Spectral data of newly prepared compounds

Compound	Spectral data[a]
IIa	^{1}H NMR ($CDCl_3$, 600 MHz), δ: 2.02 (s, 3H, $COCH_3$), 2.09 (s, 3H, $COCH_3$), 3.91–4.25 (m, 5H, CH_2O, Glcp-H-6a, Glcp-H-6b, Glcp-H-5), 4.31 (t, 1H, J = 7.2 Hz, J = 6.6 Hz, Fmoc-H-9′), 4.34–4.44 (m, 2H, Fmoc-H-10′), 4.51 (d, 1H, J = 8.4 Hz, H-2), 4.63 (brs, 1H, Glcp-H-1), 5.15–5.26 (dd, 2H, $PhCH_2$), 5.28 (t, 1H, J = 9.6 Hz, Glcp-H-4), 5.57 (d, 1H, J = 10.2 Hz, NH), 5.86 (d, 1H, J = 9.6 Hz, Glcp-H-3), 5.90 (d, 1H, J = 9.0 Hz, Glcp-H-2), 7.26–7.41 (m, 7H, H_{arom}), 7.60–7.77 (m, 7H, H_{arom}) ^{13}C NMR ($CDCl_3$, 150 MHz), δ: 20.9, 21.2, 47.5, 54.7, 63.0, 65.3, 65.8, 67.4, 67.6, 70.0, 95.5, 120.2, 125.3, 127.2, 127,3, 128.6, 128.7, 128.8, 129.0, 129.6, 131.1, 135.5, 141.5, 156.2, 170.1, 170.4, 170.9 ESI-MS, m/z: 652.0 $(M + Na)^+$
IIb	^{1}H NMR ($CDCl_3$, 600 MHz), δ: 2.02 (s, 3H, $COCH_3$), 2.09 (s, 3H, $COCH_3$), 4.01–4.11 (m, 2H, CH_2O), 4.16–4.27 (m, 4H, Fmoc-H-9′, H-2, Galp-H-6a, Gal-H-6b), 4.38–4.49 (m, 2H, Fmoc-H-10′), 4.64–4.66 (m, 1H, Galp-H-5), 4.93 (d, 1H, J = 3 Hz, Galp-H-1), 4.97–4.98 (dd, 1H, J = 1.8 Hz, J = 5.4 Hz, Galp-H-4), 5.18–5.31 (dd, 2H, $PhCH_2$), 5.78–5.80 (dd, 2H, J = 3.0 Hz, J = 10.2 Hz, Galp-H-2), 5.96 (d, 1H, J = 9.0 Hz, NH), 6.10–6.12 (dd, 1H, J = 5.4 Hz, J = 10.2 Hz, Galp-H-3), 7.31–7.43 (m, 9H, H_{arom}), 7.63 (d, 2H, J = 7.2 Hz, H_{arom}), 7.79 (d, 2H, J = 7.2 Hz, H_{arom}) ^{13}C NMR ($CDCl_3$, 150 MHz), δ: 20.6, 20.8, 46.2, 47.0, 53.4, 54.6, 62.5, 62.7, 67.2, 67.3, 69.5, 94.8, 120.0, 125.0, 125.1, 125.3, 127.0, 127.7, 128.1, 128.4, 128.5, 128.6 (2 ×), 128.7, 129.8, 135.3, 141.3, 143.7, 143.8, 155.9, 169.8, 170.2, 170.6 ESI-MS, m/z: 652.0 $(M + Na)^+$
IIc	^{1}H NMR ($CDCl_3$, 600 MHz), δ: 1.11 (d, 1H, J = 6.0 Hz, CH_3), 2.11 (s, 3H, $COCH_3$), 3.73–3.75 (m, 2H, CH_2O), 4.23–4.26 (m, 2H, Fmoc-H-9′, Rhap-H-5), 4.36–4.47 (m, 2H, Fmoc-H-10′), 4.62–4.64 (m, 1H, H-2), 4.93 (brs, 1H, Rhap-H-4), 5.01–5.03 (dd, 1H, J = 1.8 Hz, J = 9.6 Hz, Rhap-H-3), 5.19–5.26 (2H, $PhCH_2$), 5.65 (d, 1H, J = 9.6 Hz, NH), 5.75–5.77 (m, 1H, Rhap-H-2), 5.84 (brs, 1H, Rhap-H-1), 7.30–7.42 (m, 9H, H_{arom}), 7.61 (d, 2H, J = 7.2 Hz, H_{arom}), 7.77 (d, 2H, J = 7.8 Hz, H_{arom}) ^{13}C NMR ($CDCl_3$, 150 MHz), δ: 17.8, 21.1, 47.2, 54.4, 65.1, 67.2, 67.42, 68.1, 70.7, 94.5, 120.0, 125.1, 127.1, 127.7, 128.1, 128.2, 128.4, 128.6, 130.0, 135.2, 141.3, 143.7, 143.9, 170.4 ESI-MS, m/z: 571.0 (M^+)
IId	^{1}H NMR ($CDCl_3$, 600 MHz), δ: 2.08 (s, 3H, $COCH_3$), 3.59 (d, 1H, J = 13.2 Hz, Xylp-H-5a), 3.67–3.75 (m, 2H, CH_2O), 4.21–4.25 (m, 2H, Fmoc-H-9′, Xylp-H-5b), 4.36–4.47 (m, 2H, Fmoc-H-10′), 4.59–4.62 (m, 1H, H-2), 4.80 (brs, 1H, Xylp-H-4), 4.94 (d, 1H, J = 2.4 Hz, Xylp-H-1), 5.15–5.28 (dd, 2H, $PhCH_2$), 5.66 (d, 1H, J = 8.4 Hz, NH), 5.95–5.98 (m, 1H, Xylp-H-2), 6.03–6.05 (m, 1H, Xylp-H-3), 7.29–7.41 (m, 9H, H_{arom}), 7.62 (d, 2H, J = 7.2 Hz, H_{arom}), 7.77 (d, 2H, J = 7.8 Hz, H_{arom}) ^{13}C NMR ($CDCl_3$, 150MHz), δ: 21.0, 21.1, 46.3, 47.1, 54.3, 54.6, 56.15, 60.3, 61.2, 61.6, 63.0, 63.1, 63.3, 64.6, 67.2, 67.3 (2 ×), 67.4, 67.5, 68.0, 69.3, 93.1, 120.0, 125.1, 125.2, 125.4, 127.1, 127.5, 127.7, 128.19, 128.3, 128.5 (2 ×), 128.6, 128.7 (2 ×), 128.9, 129.2, 130.1, 130.6, 135.2, 141.3, 143.7, 143.9, 156.0, 170.0, 170.6 ESI-MS, m/z: 557.0 (M^+)
IIe	^{1}H NMR ($CDCl_3$, 600 MHz), δ: 2.09 (s, 3H, $COCH_3$), 3.79 (d, 1H, J = 13.2 Hz, Arap-H-5a), 3.97–4.06 (m, 3H, CH_2O, Arap-H-5b), 4.23–4.26 (m, 1H, Fmoc-H-9′), 4.35–4.46 (m, 2H, Fmoc-H-10′), 4.57–4.60 (m, 1H, H-2), 4.79 (d, 1H, J = 2.4 Hz, Arap-H-1), 4.88–4.89 (m, 1H, Arap-H-4), 5.15–5.28 (dd, 2H, $PhCH_2$), 5.74–5.76 (m, 1H, Arap-H-2), 5.84 (d, 1H, J = 9.0 Hz, NH), 6.02–6.05 (m, 1H, Arap-H-3), 7.30–7.42 (m, 9H, H_{arom}), 7.60 (d, 2H, J = 7.2 Hz, H_{arom}), 7.77 (d, 2H, J = 7.2 Hz, H_{arom}) ^{13}C NMR ($CDCl_3$, 150 MHz), δ: 21.0, 21.1, 46.6, 47.1 (2×), 53.4, 54.4, 54.6, 60.0, 61.5, 61.7, 63.0, 63.1, 64.5, 64.8, 66.0, 67.2, 67.3, 67.4, 67.6, 68.1, 68.4, 69.3, 70.0, 89.1, 90.5, 93.8, 94.3, 119.8, 120.0, 124.8, 125.1 (2 ×), 125.2, 126.8, 127.1, 127.5, 127.7, 128.1, 128.2, 128.4 (2 ×), 128.5, 128.6, 128.9, 129.6, 130.0, 130.6, 135.3, 141.3, 143.7, 143.9, 156.0, 170.0 ESI-MS, m/z: 557.0 (M^+)
IIf	^{1}H NMR ($CDCl_3$, 600 MHz), δ: 2.02 (s, 3H, $COCH_3$), 2.09 (s, 3H, $COCH_3$), 3.91–4.25 (m, 5H, CH_2O, Glcp-H-6a, Glcp-H-6b, Glcp-H-5), 4.31 (t, 1H, J = 7.2 Hz, J = 6.6 Hz, Fmoc-H-9′), 4.34–4.44 (m, 2H, Fmoc-H-10′), 4.51 (d, 1H, J = 8.4 Hz, H-2), 4.64 (brs, 1H, Glcp-H-1), 5.28 (t, 1H, J = 9.6 Hz, Glcp-H-4), 5.57 (d, 1H, J = 10.2 Hz, NH), 5.86 (d, 1H, J = 9.6 Hz, Glcp-H-3), 5.90 (d, 1H, J = 9.0 Hz, Glcp-H-2), 7.26–7.41 (m, 4H, H_{arom}), 7.60–7.77 (m, 4H, H_{arom}) ^{13}C NMR ($CDCl_3$, 150 MHz), δ: 20.9, 21.2, 47.5, 54.6, 63.0, 65.3, 65.8, 67.6, 70.0, 95.5, 120.2, 125.2, 127.7, 129.0, 129.6, 131.0, 140.9, 156.3, 170.2, 170.8, 175.2 ESI-MS, m/z: 562.6 $(M + Na)^+$
IIg	^{1}H NMR ($CDCl_3$, 600 MHz), δ: 1.34 (d, 3H, J = 6.0 Hz, CH_3), 2.07 (s, 3H, $COCH_3$), 2.08 (s, 3H, $COCH_3$), 4.02–4.06 (m, 1H, $OC\underline{H}(CH_3)$), 4.05 (d, 2H, J = 4.2 Hz, Glcp-H-6a, Glcp-H-6b), 4.23 (m, 1H, Glcp-H-5), 4.25 (t, 1H, J = 7.2 Hz, Fmoc-H-9′), 4.38–4.46 (m, 3H, Fmoc-H-10′, H-2), 4.72 (brs, 1H, Glcp-H-1), 5.12–5.27 (m, 4H, $PhCH_2$, Glcp-H-4, NH), 5.49 (d, 1H, J = 10.2 Hz, Glcp-H-3), 5.76 (d, 1H, J = 10.2 Hz, Glcp-H-2), 7.26–7.61 (m, 9H, H_{arom}), 7.63 (d, 2H, J = 6.6 Hz, H_{arom}), 7.77 (d, 2H, J = 7.8 Hz, H_{arom}) ^{13}C NMR ($CDCl_3$, 150 MHz), δ: 20.9, 21.2, 47.5, 54.7, 63.0, 65.3, 65.8, 67.4, 67.6, 70.0, 95.5, 120.2, 125.3, 127.2, 127.3, 127.9, 128.6, 128.7, 128.8, 129.0, 129.6, 131.1, 135.5, 141.5, 156.2, 170.1, 170.4, 170.9 ESI-MS, m/z: 644.2 $(M + H)^+$, 666.2 $(M + Na)^+$

Table 2. (continued)

Compound	Spectral data[a]
IIh	^{1}H NMR ($CDCl_3$, 600MHz), δ: 2.00 (s, 3H, $COCH_3$), 2.06 (s, 3H, $COCH_3$), 3.61 (m, 2H, H-3), 4.06 (m, 2H, Glcp-H-6a, Glcp-H-6b), 4.20 (m, 1H, Glcp-H-5), 4.27–4.37 (m, 2H, Fmoc-H-9′, Fmoc-H-10′a), 4.43 (dd, 1H, J = 7.2 Hz, J = 10.8 Hz, Fmoc-H-10′b), 4.68 (d, 1H, J = 7.8 Hz, H-2), 5.11–5.24 (m, 3H, $PhCH_2$, Glcp-H-4), 5.40 (d, 1H, J = 9.6 Hz, NH), 5.62 (brs, 1H, Glcp-H-1), 5.96–6.04 (m, 2H, Glcp-H-3, Glcp-H-2), 6.93 (dd, 2H, J = 8.4 Hz, Tyr-H_{arom}), 7.29–7.41 (m, 11H, H_{arom}), 7.56 (d, 2H, J = 6.0 Hz, H_{arom}), 7.77 (d, 2H, J = 7.8 Hz, H_{arom}) ^{13}C NMR ($CDCl_3$, 150MHz), δ: 20.7, 21.0, 29.7, 37.2, 47.2, 54.8, 55.0, 61.9, 62.6, 63.6, 65.0, 67.0, 67.8, 69.2, 70.5, 76.8, 77.0, 77.2, 93.1, 117.1, 120.01, 125.1, 126.5, 127.1, 127.7, 128.5, 128.6, 128.7, 130.2, 130.43, 133.0, 140.9, 147.6, 149.7, 170.5, 170.9, 172.0 ESI-MS, m/z: 706.2 $(M + H)^+$, 729.2 $(M + Na)^+$

a) When reporting assignments of ^{1}H NMR signals, data for protons of Fmoc amino acids moiety are identified by a prime; abbreviations used refer to saccharide moiety: Glcp – glucopyranose, Galp – galactopyranose, Rhap – rhamnopyranose, Xylp – xylopyranose, Arap – arabinopyranose; brs means broad singlet; H_{arom} means aromatic protons.

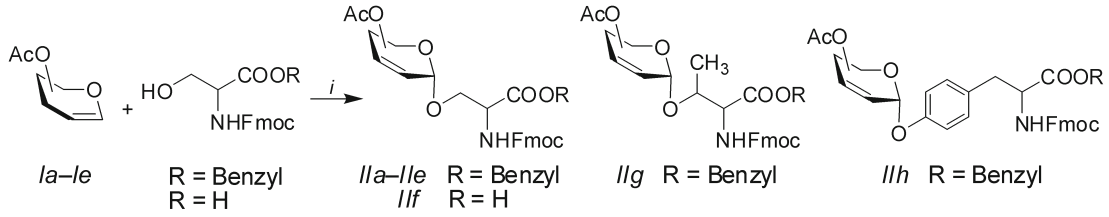

Fig. 1. Synthesis of *O*-glycosylated amino acid based on glycals. Reaction conditions: *i*) I_2, CH_2Cl_2, ambient temperature, 0.5–1 h. For the designation of individual compounds *Ia–Ie* and *IIa–IIh*, see Experimental.

3,4,6-tri-*O*-acetyl-D-glucal (*Ia*) with Fmoc-Ser-OBn as a model. Firstly, various amounts of I_2 were used and the progress of the reaction was monitored by TLC. It was noted that the glycosylation proceeded smoothly with 50 mole % of I_2 in CH_2Cl_2 at ambient temperature with short reaction times, affording the corresponding alkyl 2,3-unsaturated glycosides with good to high yields. Based on the value of the coupling constant of the anomeric H atom ($J_{1,2}$ = 0 Hz) and chemical shift of the anomeric C atom (δ 95.48) obtained from the NMR spectra, it is evident that the α-anomers are produced exclusively (Table 2).

Subsequently, various Lewis and Brønsted acids used as promoters were investigated; the details are summarised in Table 3. The glycosylation products were complex and difficult to purify when the $BF_3 \cdot Et_2O$ complex, trifluoroacetic acid (TFA) or $SnCl_4$ were used as the promoter (entries 3, 4, 5, Table 3). It was presumed that the strong acidity of these promoters caused decomposition of the substrates at ambient temperature, hence, an attempt was made to perform the reaction at –40 °C. However, the reaction still did not proceed and the protected amino acid was not fully consumed. When $FeCl_3$ was used, no product was detected (entry 6). It is worth noting that when *N*-iodosuccinimide (NIS) was used as the promoter, the starting amino acid continued to be present even after two days; extending the reaction time yielded a complex product mixture (entry 2). Along with the desired product *IIa* isolated with a low yield (32 %), a trace amount of *O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-iodo-α-D-mannopyranosyl)-*N*-(9-fluorenylmethoxycarbonyl)-L-serine benzyl ester was also observed (Hoffmann et al., 1997). These results indicate that I_2 was superior to other catalysts in terms of yield and stereoselectivity.

Table 3. Screening of conditions for promoter-mediated Ferrier reaction of 3,4,6-tri-*O*-acetyl-D-glucal (*Ia*) with Fmoc-Ser-OBn

Entry	Promoter	Product *IIa*	
		Yield/%	α/β anomer ratio
1	I_2	88	> 9 : 1
2	NIS	32	nd
3	$BF_3 \cdot Et_2O$	nd	nd
4	TFA	nd	nd
5	$SnCl_4$	nd	nd
6	$FeCl_3$	0	–

nd – not determined due to complex mixture of reaction products.

Under the optimised conditions, the scope of this method for the synthesis of 2,3-unsaturated-*O*-glycosides using various glycals and protected amino acids was explored (Table 4). It was found that per-*O*-acetylated galactal (*Ib*) and rhamnal (*Ic*) gave good yields and anomer selectivities (entries 1, 2), whereas per-*O*-acetylated xylal (*Id*) and arabinal (*Ie*) afforded only moderate yields but with good anomer selectiv-

Table 4. Scope of I_2-mediated Ferrier reaction of per-*O*-acetylated glycals

Entry	Reactants		Product		
	Amino acid	Glycal	*II*	Yield/%	α/β anomer ratio
1	Fmoc-Ser-OBn	*Ib*	*IIb*	83	> 9 : 1
2	Fmoc-Ser-OBn	*Ic*	*IIc*	89	> 9 : 1
3	Fmoc-Ser-OBn	*Id*	*IId*	56	> 9 : 1
4	Fmoc-Ser-OBn	*Ie*	*IIe*	54	> 9 : 1
5	Fmoc-Ser-OH	*Ia*	*IIf*	20	> 9 : 1
6	Fmoc-Thr-OBn	*Ia*	*IIg*	86	> 9 : 1
7	Fmoc-Thr-OH	*Ia*	–	trace	–
8	Fmoc-Tyr-OBn	*Ia*	*IIh*	33	> 9 : 1
9	Fmoc-Tyr-OH	*Ia*	–	trace	–

ities (entries 3, 4). Also, the glycosylation of Fmoc-Thr-OBn and Fmoc-Tyr-OBn was proved to be effective (entries 6, 8). Glycosylation of Fmoc amino acids without prior protection of the carboxyl groups using similar conditions was also attempted but only low yields or a trace amount of products were obtained (entries 5, 7, 9). In addition, the type of hydroxyl group exerted a significant influence on the glycosylation reaction. The activity of the phenol hydroxyl was very poor and only low or trace amounts of the product were detected (entries 8, 9).

Conclusions

An efficient method for the synthesis of glycosylated Fmoc amino acid building blocks from glycals was developed. The I_2-mediated Ferrier reaction using Fmoc amino acids having protected or unprotected carboxyl groups was shown to serve as a powerful glycosylation method in the formation of *O*-glycosylated amino acid with high yield and high α-stereoselectivity. To the best of our knowledge, this is the first example of the glycosylation of Fmoc amino acids with appropriate *O*-protected glycals; it can have extensive applications in the synthesis of *O*-glycopeptides/proteins. Further studies on this reaction in the production of other glycosylated Fmoc amino acids, as well as in the solid support synthesis of glycopeptides, are in progress.

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