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Neo-glycoconjugates: stereoselective synthesis of α-glycosyl amides via Staudinger ligation reactions

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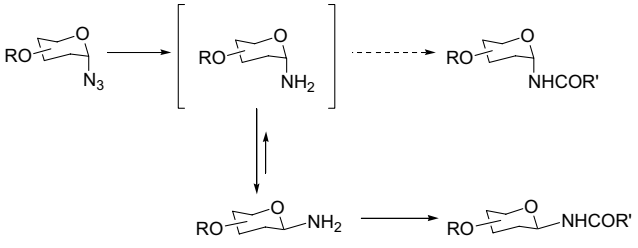
Abstract—α-Glycosyl azides can be transformed in the corresponding α-glycosyl amides with good yields and selectivity via reduction–acylation (Staudinger ligation) reactions using funtionalised phosphines **1a**–**f**. The limits and scope of this approach for the synthesis of α-glycosyl amides are reported.

1. Introduction

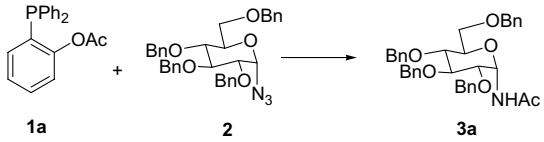
It has been recently shown that the conformation of the peptide in α- and β-*N*-linked glycopeptides is uniquely influenced by the attached sugar in ways that depend on the configuration of the carbohydrate–peptide linkage.[1] The stereoselective synthesis of neo-glycoconjugates in the 'unnatural' α configuration has therefore become of great interest as a means of designing glycopeptide mimetics, which can be useful as probes or inhibitors of glycosyltransferases. The stereoselective synthesis of α-glycosyl amides has proven difficult because glycosyl amines are not configurationally stable and undergo easy anomerisation (Scheme 1).



Scheme 1. α → β Isomerisation of anomeric amines precludes the stereoselective synthesis of α-glycosyl amides.

Various methods have been proposed to circumvent this process, which destroys the stereochemical integrity of the product, and to synthesise α-glycosyl amides avoiding the formation of the intermediate free amines.[2–7] Much work has been devoted to the Staudinger ligation reaction, that is, the reduction of glycosyl azides with trialkyl or triarylphosphines in the presence of carboxylic acids or derivatives, which can trap the aza-ylide (iminophosphorane) intermediate before the free amine is formed. However, in most cases, anomerisation remains a significant problem also for Staudinger intermediates and β-amides or mixtures of anomers are obtained.[5]

We have recently reported[8] the first general methodology for reductive acetylation of α-glycosyl azides that proceeds with complete retention of configuration at the anomeric carbon using the functionalised phosphine **1a**.[9,10] The reaction could be applied to *O*-benzyl glycosyl azides in the fuco-, gluco- and galacto-series with good yield and selectivity (Scheme 2).[8]



Scheme 2. Stereoselective synthesis of α-glycosyl acetamides.

We have now explored the limits and scope of this approach for the synthesis of other α-glycosyl amides and our results are reported herein.

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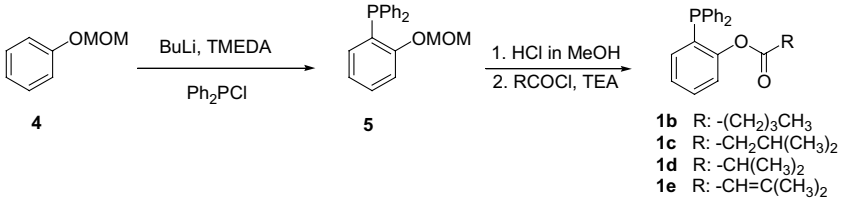
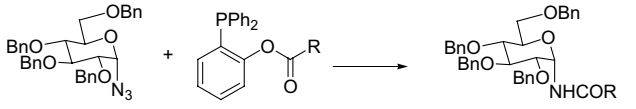


Scheme 3. Synthesis of acyl phosphines **1b–e**.

2. Results and discussion

The functionalised phosphines **1b–e** (Scheme 3) were synthesised as previously reported[8–11] starting from *o*-diphenylphosphinophenol. All the reagents are easily synthesised and handled, and can be conserved at 4 °C for several weeks, either pure or as a 1 M solution in toluene.

The α-glucosyl azide **2** was chosen as the model substrate for the Staudinger ligation reaction (Scheme 4). Our previous studies had shown[8] that **2** reacts with **1a** in various solvents (CCl_4, toluene, $CHCl_3$) to give the α-glucosyl acetamide **3a** in 77% yield after 24 h at 70 °C. Under the same conditions the reaction between **2** and the *n*-pentanoate **1b** afforded only 24% of the expected *n*-pentanamide **3b**. The major reaction product was a stable, phosphorus-containing intermediate, which could be isolated by flash chromatography on silica gel. Once purified, the intermediate spontaneously evolved to the desired α-pentanamide **3b** in a few hours at room temperature, but the transformation could not be induced in the reaction mixture under various conditions of solvent (CCl_4, $CHCl_3$, toluene), temperature, or time (up to 36 h at 70 °C).

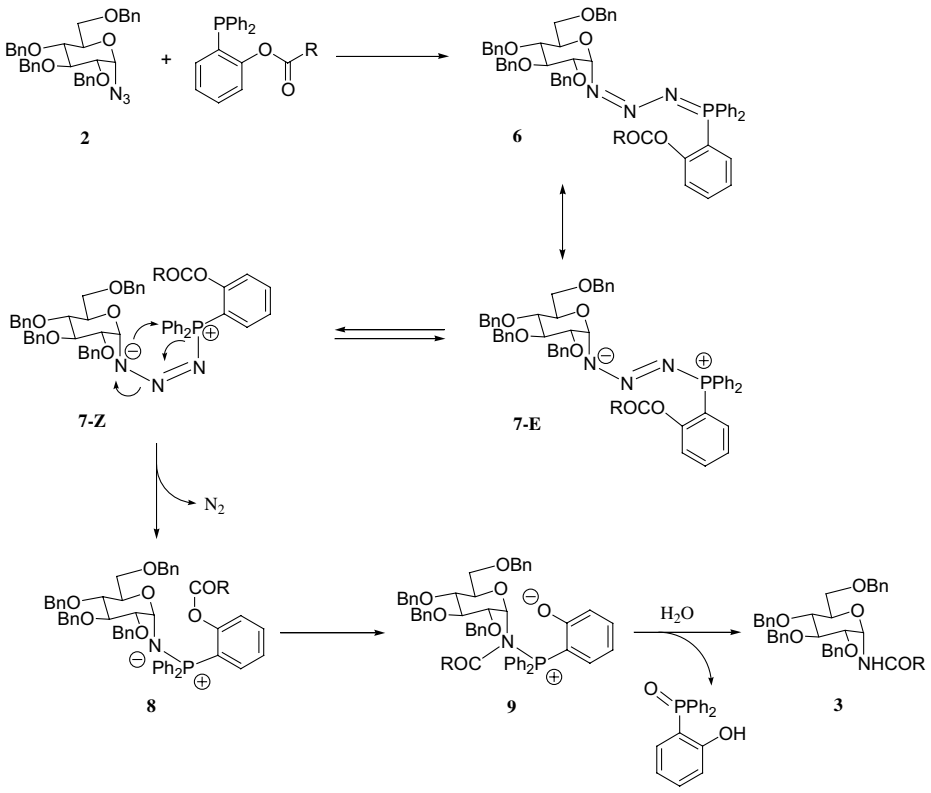


Scheme 4. Staudinger ligation of 1-azido-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose **2** with phosphines **1b–e**.

NMR analysis of the isolated intermediate revealed two compounds, **M** and **m**, in 84:16 ratio. The two compounds could not be separated by chromatography and, once isolated, appeared (by NMR spectroscopy) to transform to the final product without appreciable modification of their initial ratio. In the ^{31}P NMR spectrum the major isomer **M** is characterised by a signal at 27.4 ppm. In the ^{1}H NMR spectrum its anomeric proton appears as a doublet at 5.07 ppm ($J_{H1-H2} = 4.1$ Hz) correlated in the Hetcor ^{1}H–^{13}C spectrum to a peak at 83.5 ppm. Neither the anomeric proton (H-1) nor the anomeric carbon (C-1) display any correlation to the ^{31}P signal, as shown in the Hetcor ^{1}H–^{31}P spectrum (no cross-peak) and in the proton decoupled ^{13}C NMR APT spectrum (a singlet for C-1). Similarly, the minor compound **m** shows a broad doublet at 5.36 ppm ($J_{H1-H2} = 4.1$ Hz) for H-1 correlated to a peak at 80.1 ppm for C-1 in the ^{13}C spectrum. The phosphorus nucleus of **m** gives a signal at 27.1 ppm, which shows no correlation to H-1 or C-1.

The accepted mechanism for the Staudinger reduction of azides with phosphines[12] requires the formation of two different intermediates: initially, a phosphotriazene (phosphotriazadiene) is formed by nucleophilic attack of phosphorus on the distal nitrogen of the azide (Scheme 5, **6**). This intermediate is stabilised by electron donating groups on the phosphine, or electron withdrawing groups on the azide, or sterically hindering groups on both phosphine and azide.[13] Phosphotriazadienes have been isolated from Staudinger azide reductions and characterised by X-ray crystallography and other techniques:[5,12–14] they all have been found to be consistent with a zwitterionic structure corresponding to **7** (Scheme 5) displaying a partial double bond character of the central N–N linkage. The *E* configuration of the N–N double bond (Scheme 5, **7-*E***) is generally observed. In the reaction mixture **7-*E*** can isomerise to the *Z* isomer **7-*Z***, which spontaneously decomposes to afford N_2 and the iminophosphorane **8**. Glycosyl iminophosphoranes are rather stable, and some have been isolated and characterised by NMR spectroscopy.[5] In the presence of acylating agents, the iminophosphorane reacts at nitrogen, to give, after hydrolysis, the corresponding amide. In the present case, intramolecular trapping of the iminophosphorane should occur to afford **9**. Likely, this process is faster than anomeric equilibration of **8**, thus allowing for retention of the anomeric configuration of the starting azide. Decomposition of **9**, either spontaneous or induced by water quenching, affords the desired α-glycosylamide **3** and the phosphinoxide by-product.

The NMR data collected for the intermediate **M** and **m** in the reaction between **2** and **1b** are consistent with the phosphotriazadiene structure **7**, because no coupling is observed between the phosphorus nucleus and either the anomeric proton or carbon. Coupling constants J_{C1-P} and J_{H1-P} of ca. 20 Hz have been reported in the literature for glycosyl iminophosphoranes.[5] The J_{H1-H2} values observed for both intermediates is of ca. 4 Hz, consistent with the expected value for a *cis* relationship between H-1 and H-2 in both compounds. Hence **M** and **m** do not appear to be anomeric epimers of **7**. It is therefore likely that the two compounds correspond to the



Scheme 5. Proposed mechanism for the intramolecular Staudinger ligation of **2**.

two isomers **7-*E*** and **7-*Z*** of the phosphotriazadiene intermediate. MALDI and ESI mass spectrometry show for the 84:16 **M** and **m** mixture a single molecular ion at *m*/*z* 922.3 ($M+Na^+$), which is consistent with the iminophosphorane structure. However, considering the results of the NMR analysis, it is likely that this compound is obtained in the spectrometer upon ionisation-induced nitrogen loss.

Although this partial analysis was not sufficient to fully characterise the reaction intermediates, it suggested that the phosphotriazadiene–iminophosphorane rearrangement and nitrogen loss, that appeared to occur spontaneously and at room temperature from the isolated triazadiene, is inhibited by some unknown element in the reaction mixture. Efforts to identify the inhibiting agent or to accelerate the nitrogen loss by increasing the reaction temperature, or by providing acid catalysis (to accelerate *E* to *Z* isomerisation of the phosphotriazadiene) were unsuccessful. We found, however, that sunlight appeared to accelerate the decomposition of the intermediates, and indeed when the Staudinger ligation of **2** with **1b** was carried out in $CHCl_3$, at 70 °C and under an ordinary sunlamp (Philips HPL 250 W, mercury with magnesium arsenate), clean conversion to the product amide **3b** occurred in 1 h. After flash chromatography, the reaction product was isolated in 60% yield as a 84:16 α/β mixture. Under the same conditions, conversion could be obtained also with the other phosphines **1c**–**e** (see Table 1) to give the corresponding α-amides in good to moderate yields. The reaction appears to be rather sensitive to steric and electronic factors. For instance, synthesis of the *i*-butanamide **3d** required a much longer irradiation time (24 h) to achieve modest yields (40%). On the contrary, the 3,3-dimethylacriloyl substituted phosphine **1e** reacted much faster with **2** and the reaction product **3e** could be obtained also without irradiation (data not shown).

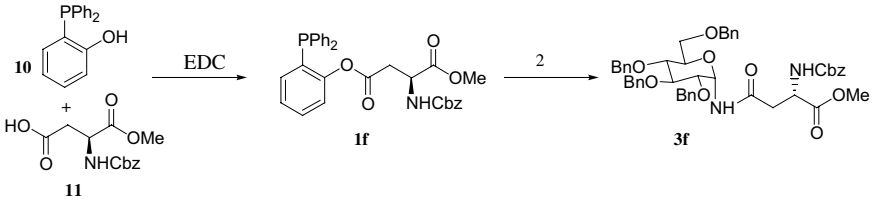
Table 1. Staudinger ligation of the glycosyl azide **2** with phosphines **1b**–**e**[a]

Phosphine	Product	Yield (%)	α/β ratio[b]
1b	**3b**	60	84:16
1c	**3c**	70	83:17
1d	**3d**	40[c]	84:16
1e	**3e**	65	85:15

[a] Reactions were run at 70 °C in $CHCl_3$ (0.1 M). After disappearance of the starting material (ca. 1 h), the mixtures were irradiated with a sunlamp for 1 h at 70 °C.
[b] Determined by ^1H NMR.
[c] After 24 h irradiation. 15% of triazadiene intermediate was also isolated.

In all cases, the α-amide was the prevailing product in the reaction crude, as judged by ^1H NMR. Chromatographic purification of the α isomer was generally possible using flash chromatography. Amides **1b**–**e** (like **1a**) appear to adopt a $^4C_1$ conformation, and their anomeric configuration could be assigned based on the H1–H2 coupling constant, which is, in all cases of ca. 5 Hz.

N-Linked glycopeptides are connected to the peptide aglycon via the side chain of an Asn residue.[15]



Scheme 6. Synthesis of **3f**.

N-Glycosylation of aspartic acid side chain appears therefore particularly useful to obtain neo-glycopeptides. For this purpose *o*-diphenylphosphinophenol **10** was acylated with Cbz-L-aspartic acid 1-methyl ester **11** using *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (EDC) as the condensing agent. The corresponding acyl phosphine **1f** was used for the reduction–acylation of **2** (Scheme 6).

In this case, acyl transfer appeared to be particularly sluggish. After 10 h irradiation at 70 °C in toluene, only 10–20% of **3f** was isolated together with a 1:1 mixture of two intermediates. NMR spectroscopy of the intermediates showed two anomeric protons: the first one as a doublet at 5.35 ppm (J_{H1-H2} = 4.1 Hz) with no correlation with the phosphorous atom (no cross-peak in the Hetcor ^{1}H–^{31}P spectrum), the second one as a doublet of doublets at 4.92 ppm with $J_{H1-H2} = J_{H1-P}$ = 1.5 Hz. This value for the J_{H1-P} coupling constant is not consistent with an iminophosphorane structure.[5] Therefore the two isolated intermediates could be again assigned as the two phosphotriazadiene isomers. This hypothesis was confirmed by the analysis of the ^{13}C NMR spectrum, which showed two singlets (at 80.2 and 82.6 ppm) for the two anomeric carbons.

Further experimentation failed to uncover appropriate conditions to induce the transfer in the reaction mixture.[†] However, as already observed in the synthesis of **3b**, also in this case conversion of the intermediates occurred spontaneously after chromatographic isolation. Thus the best conditions for conversion of **2** in **3f** involve treatment with **1f** at 70 °C for 1 h, followed by chromatographic isolation of the intermediates, which are then converted to **3f** (86:14 α/β) by stirring over night in $CHCl_3$ (75% yield from **2**).

3. Conclusion

In conclusion, phosphines **1** have been shown to be general-scope Staudinger ligation agents for α-glycosyl azides and to afford the corresponding α-amides with good stereoselectivity for a broad range of acyl chains. Thus the first general method for the stereoselective synthesis of α-glycosyl amides from the corresponding α-azides has been established. Steric hindrance of the acyl chain to be ligated appears to slow down the reaction, whereas transfer of unsaturated acyl chains appears to be very facile. The low reactivity of the acylating agent can often be overcome by irradiating the reaction mixture with a simple sunlamp. When irradiation fails to achieve the desired effect, the most efficient procedure for the Staudinger ligation consists in isolating the reaction intermediate (likely, a mixture of phosphotriazadienes) and allowing it to evolve spontaneously to the amide products.

4. Experimental

Solvents were dried by standard procedures. Solvents used to synthesise and manipulate phosphines were degassed and saturated with Ar. Reactions requiring anhydrous conditions were performed under Ar. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded at 300 K, unless otherwise noted, on a Bruker AVANCE-500, Bruker AVANCE-400 or Bruker AC-200 spectrometer. Chemical shifts δ for ^{1}H and ^{13}C are expressed in ppm relative to internal Me_4Si as standard. Chemical shifts δ for ^{31}P are expressed in ppm relative to internal H_3PO_4 as standard. Signals were abbreviated as s, singlet; bs broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Mass spectra were obtained with a MALDI-TOF (OMNIFLEX Bruker) or an ESI (LCQ Advantage Termofinnigan) apparatus. Optical rotations were measured in a cell of 1 dm pathlength and 1 mL capacity with a Perkin–Elmer 241 polarimeter. IR spectra were recorded on a JASCO FT/IR-300E spectrometer, and frequencies are expressed in cm^{-1}. Thin layer chromatography (TLC) was carried out with precoated Merck F_{254} silica gel plates. Flash chromatography (FC) was carried out with Macherey–Nagel silica gel 60 (230–400 mesh). The *O*-benzyl glucosyl azide **2**,[8,16] the methoxymethylphenyl ether **4**[17] and the phosphine **5**[11a] were synthesised as described in the literature.

4.1. Synthesis of the *o*-diphenylphosphinophenol 10

Five millilitres of dry methanol were saturated with gaseous HCl. Methoxymethyl *o*-diphenylphosphinophenyl ether **5** (760 mg, 2.36 mmol) was added at room temperature and under Ar. The resulting solution was stirred for 1 h then the solvent was evaporated giving a yellow oil. The residue was dissolved in AcOEt and washed with saturated $NaHCO_3$.[11b] The organic layer was dried over Na_2SO_4 and concentrated. The residue was dissolved in dry MeOH (3 mL), then water was added until the cloud point was reached. The solution was stirred under Ar while cooling, and the resulting white solid was filtered

[†] The conditions tried include: increasing the reaction temperature to 110 °C, changing the solvent from toluene to $CHCl_3$, irradiating the mixture at 70 °C with a Xenon lamp, using different protecting groups on the amino acid.

to give **10** in 77% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 7.43–7.26 (m, 11H), 7.05–6.86 (m, 3H), 6.42 (bs, 1H, O*H*). ^{31}P NMR (160 MHz, $CDCl_3$): −26.6 (+40.7 oxide).

4.2. General procedure for the synthesis of the 2-diphenylphosphanyl-phenyl esters 1b–e

To a solution of the *o*-diphenylphosphinophenol **10** (1 equiv) in dry CH_2Cl_2 (0.1 M) at room temperature and under Ar, dry Et_3N (1.1 equiv) and the acyl chloride (1.1 equiv) were added. The reaction mixture was stirred at room temperature and monitored by TLC (9:1 hexane/AcOEt) until disappearance of **10** (ca. 1 h). The solvent was then evaporated under reduced pressure and the residue was diluted with AcOEt and extracted with 5% $NaHCO_3$ and water. The organic layer was dried over Na_2SO_4 and concentrated. The crude product was used for the Staudinger ligation. Analytical samples were purified by flash chromatography using 8:2 hexane/AcOEt as the eluent.

4.2.1. 2-Diphenylphosphanyl-phenyl pentanoate 1b. Yield = 96%; ^{1}H NMR (400 MHz, $CDCl_3$): 7.40–7.31 (m, 11H), 7.19–7.12 (m, 2H), 6.86–6.82 (m, 1H), 2.28 (t, 2H, CH_2, J = 7.5 Hz), 1.51 (m, CH_2), 1.29 (m, CH_2), 0.89 (t, 3H, CH_3, J = 7.5 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$): 171.8, 153.2, 134.7, 134.5, 134.0, 133.9, 133.8, 132.2, 131.8, 130.1, 129.2, 128.9, 128.8, 128.7, 126.2, 125.9, 125.7, 122.8, 33.9, 26.7, 22.3, 13.9; ^{31}P NMR (161 MHz, $CDCl_3$): −14.8 (+27.2 oxide).

4.2.2. 2-Diphenylphosphanyl-phenyl 3-methyl-butanoate 1c. Yield = 97%; ^{1}H NMR (400 MHz, $CDCl_3$): 7.42–7.32 (m, 11H), 7.20–7.12 (m, 2H), 6.88–6.83 (m, 1H), 2.17 (d, 2H, CH_2, J = 7.0 Hz), 2.05 (m, 1H, CH), 0.94 (d, 6H, $2CH_3$, J = 7.0 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$): 171.1, 134.2, 133.9, 132.0, 131.8, 130.1, 129.2, 128.9, 128.8, 128.7, 126.2, 122.74, 122.71, 43.0, 25.5, 22.6; ^{31}P NMR (161 MHz, $CDCl_3$): −15.0 (+27.1 oxide).

4.2.3. 2-Diphenylphosphanyl-phenyl *i*-butanoate 1d. Yield = 87%; ^{1}H NMR (400 MHz, $CDCl_3$): 7.42–7.26 (m, 11H), 7.18–7.12 (m, 2H), 6.83–6.78 (m, 1H), 2.55 (m, 1H, CH, J = 7.0 Hz), 1.10 (d, 6H, $2CH_3$, J = 7.0 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$): 175.0, 134.4, 133.8, 130.1, 129.2, 129.1, 128.8, 128.7, 126.2, 122.64, 122.61, 34.3, 18.82, 18.80; ^{31}P NMR (161 MHz, $CDCl_3$): −15.05 (+28.9 oxide).

4.2.4. 2-Diphenylphosphanyl-phenyl 3-methyl-but-2-enoate 1e. Yield = 84%; ^{1}H NMR (400 MHz, $CDCl_3$): 7.43–7.32 (m, 11H), 7.22–7.12 (m, 2H), 6.93–6.86 (m, 1H), 5.69 (m, 1H, C*H*=C$(CH_3)_2$), 2.09 (d, 3H, CH_3, J = 1.2 Hz), 1.90 (d, 3H, CH_3, J = 1.2 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$): 164.3, 159.9, 134.4, 134.0, 133.83, 183.80, 130.0, 129.0, 128.8, 128.7, 128.6, 128.5, 126.0, 123.04, 122.99, 115.0, 27.7, 20.6; ^{31}P NMR (161 MHz, $CDCl_3$): −14.8 (+26.8 oxide).

4.3. Synthesis of 1f

To a suspension of EDC·HCl (1.4 equiv) and dry *i*-Pr_2EtN (1.4 equiv) in dry CH_2Cl_2, a solution of the *o*-diphenylphosphinophenol **10** (1 equiv), the protected amino acid **11** (1.2 equiv) and DMAP (0.1 equiv) in dry CH_2Cl_2 (0.1 M) was added, at room temperature and under Ar. The mixture was stirred at room temperature for 2 h, monitoring by TLC (6:4 hexane/AcOEt). The reaction mixture was diluted with CH_2Cl_2 and extracted with 10% HCl and water: the organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography using 6:4 hexane/AcOEt as the eluent to afford **1f** in 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 7.39–7.24 (m, 11H), 7.17–7.08 (m, 2H), 6.86 (m, 1H), 5.77 (d, 1H, N*H*, J = 8.9 Hz), 5.17 (d, 1H, CH_2–Ph, J = 12.3 Hz), 5.12 (d, 1H, CH_2–Ph, J = 12.3 Hz), 4.61 (m, 1H, C*H*), 3.70 (s, 3H, COOMe), 3.04 (dd, 1H, CH_2–COO, J = 5.1, 17.4 Hz), 2.75 (dd, 1H, CH_2–COO, J = 4.4, 17.0 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$): 171.1, 169.3, 156.2, 152.8, 152.5, 136.4, 135.6, 135.5, 135.4, 135.3, 134.3, 134.2, 133.91, 133.88, 130.5, 130.3, 130.2, 129.4, 129.3, 128.9, 128.8, 128.7, 128.4, 128.3, 126.7, 122.61, 122.57, 67.3, 53.0, 50.4, 36.6; ^{31}P NMR (161 MHz, $CDCl_3$): −15.65 (+28.2 oxide).

4.4. General procedure for the synthesis of the α-glucosyl amides 3b–e

To a solution of **2** (1 equiv) in $CHCl_3$ (0.1 M) a 1 M solution in dry toluene of the acylphosphine **1b–e** (1.2 equiv) was added. The mixture was heated to 70 °C for 1 h (until disappearance of **2** from the TLC plate; 8:2 toluene/AcOEt) and then irradiated for 1 h with a Philips HPL 250W sunlamp (24 h for product **3d**). The crude was diluted with AcOEt, stirred with H_2O for a few minutes, then the phases were separated and the organic layer washed with water. The solution was dried over Na_2SO_4, and the solvent evaporated to yield crudes that were purified by flash chromatography (7:3 petroleum ether/AcOEt) to give the α-glucosyl amides with the yields and anomeric ratios reported in Table 1.

4.4.1. 3b. ^{1}H NMR (400 MHz, $CDCl_3$): 7.43–7.12 (m, 20H, aromatics), 6.09 (d, 1H, N*H*, $J_{1\text{-NH}}$ = 6.8 Hz), 5.85 (dd, 1H, H_1, $J_{1\text{-NH}}$ = 6.8 Hz, $J_{1\text{–}2}$ = 5.5 Hz), 4.97–4.79 (m, 4H, –CH_2Ph), 4.69–4.47 (m, 4H, –CH_2Ph), 3.88–3.60 (m, 6H, H_2, H_3, H_4, H_5, H_6 and $H_{6'}$), 2.25 (t, 2H, –CH_2–, J = 6.8 Hz), 1.64 (m, 2H, –CH_2–), 1.37 (m, 2H, –CH_2–), 0.92 (t, 3H, –CH_3, J = 6.8 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$): 174.2, 138.7, 138.2, 137.4, 129.9, 128.8, 128.6, 128.4, 128.3, 128.2, 128.0, 127.9, 82.3, 75.7, 75.3, 74.5, 73.8, 72.7, 71.3, 68.5, 36.8, 29.9, 27.8, 22.6, 14.0; ESI-MS: 646.6 ($M+Na^+$); IR (Nujol): 3426, 1654; $[\alpha]_D^{25}$ = +47.6 (*c* 1.0, $CHCl_3$).

4.4.2. 3c. ^{1}H NMR (400 MHz, $CDCl_3$): 7.38–7.14 (m, 20H, aromatics), 6.21 (d, 1H, N*H*, $J_{1\text{-NH}}$ = 6.7 Hz), 5.88 (dd, 1H, H_1, $J_{1\text{-NH}}$ = 6.7 Hz, $J_{1\text{–}2}$ = 5.0 Hz), 4.98–4.49 (m, 8H, –CH_2Ph), 3.90–3.63 (m, 6H, H_2, H_3, H_4, H_5, H_6 and $H_{6'}$), 2.20–2.11 (m, 3H, –CH_2– and –CH–), 0.97 (d, 6H, 2 –CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$): 173.5, 138.5, 138.1, 137.3, 128.8, 128.6, 128.4, 128.1, 128.0, 127.8, 127.7, 86.2, 82.1, 77.6, 77.5, 76.5, 75.5, 75.2, 74.6, 74.5, 73.6, 72.5, 71.2, 68.3, 46.1, 26.2, 22.5;

ESI-MS 624.5 ($M+H^+$), 646.7 ($M+Na^+$), 662.5 ($M+K^+$); IR (Nujol): 3383, 1652; $[\alpha]_D^{25} = +56.3$ (*c* 0.5, $CHCl_3$).

4.4.3. 3d. ^1H NMR (400 MHz, $CDCl_3$): 7.37–7.12 (m, 20H, aromatics), 6.12 (d, 1H, N*H*, $J_{1\text{-NH}} = 6.6$ Hz), 5.83 (dd, 1H, H_1, $J_{1\text{-NH}} = 6.6$ Hz, $J_{1-2} = 5.0$ Hz), 5.01–4.43 (m, 8H, –CH_2Ph), 3.93–3.58 (m, 6H, H_2, H_3, H_4, H_5, H_6 and $H_{6'}$), 2.42 (m, 1H, H_α), 1.25 (d, 6H, 2–CH_3, $J_{CH_3\text{-}\alpha} = 6.9$ Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$): 178.1, 138.6, 138.2, 137.4, 128.8, 128.62, 128.55, 128.34, 128.26, 128.2, 128.0, 127.93, 127.86, 82.2, 78.8, 77.1, 75.7, 75.3, 74.8, 73.8, 72.6, 71.3, 68.4, 36.0, 19.7, 19.6; ESI-MS: 610.4 ($M+H^+$), 632.6 ($M+Na^+$); IR (Nujol): 3421, 1646; $[\alpha]_D^{25} = +46.2$ (*c* 0.5, $CHCl_3$).

4.4.4. 3e. ^1H NMR (400 MHz, $CDCl_3$, 328 K) 7.33–7.22 (m, 20H, aromatics), 6.01 (d, 1H, N*H*, $J_{1\text{-NH}} = 6.85$ Hz), 5.82 (bs, 1H, H_1), 5.64 (m, 1H, H_b), 4.93–4.86 (m, 1H, –CH_2Ph), 4.81–4.76 (m, 2H, –CH_2Ph), 4.63–4.46 (m, 5H, –CH_2Ph), 3.82 (dd, 1H, H_2, $J_{1-2} = 5.4$ Hz, $J_{2-3} = 9.3$ Hz), 3.79–3.63 (m, 5H, H_3, H_4, H_5, H_6 and $H_{6'}$), 2.17 (s, 3H, CH_3), 1.85 (s, 3H, CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$): 167.5, 154.2, 138.7, 138.3, 138.2, 137.2, 129.1, 128.7, 128.60, 128.56, 128.3, 128.2, 128.1, 128.0, 127.94, 127.90, 117.9, 82.4, 78.0, 77.2, 75.7, 75.3, 74.9, 73.8, 72.6, 71.2, 68.5, 27.6; ESI-MS: 622.4 ($M+H^+$), 644.5 ($M+Na^+$), 660.3 ($M+K^+$); IR (Nujol): 3419, 1634; $[\alpha]_D^{25} = +74.1$ (*c* 1.0, $CHCl_3$).

4.5. Synthesis of 3f

To a solution of **2** (1 equiv) in dry toluene (0.1 M) a 1 M solution in dry toluene of the acylphosphine **1f** was added (1.2 equiv). The mixture was heated to 70 °C for ca. 1 h, until disappearance of **2** from the TLC plate (8:2 toluene/AcOEt). The solvent was evaporated and the intermediates isolated by flash chromatography (7:3 toluene/AcOEt). The isolated intermediates were stirred overnight at room temperature in $CHCl_3$, before adding water. The mixture was diluted with AcOEt, the phases separated. The organic phase was washed with water, dried over Na_2SO_4 and evaporated. The crude was purified by flash chromatography (8:2 toluene/AcOEt) to afford **3f** as a 86:14 α/β mixture in 75% yield. ^1H NMR (400 MHz, $CDCl_3$): 7.40–7.21 (m, 23H, aromatics), 7.13–7.11 (m, 2H, aromatics), 6.33 (d, 1H, N*H*, $J = 6.3$ Hz), 5.99 (d, 1H, N*H*, $J = 8.1$ Hz), 5.68 (dd, 1H, H_1, $J = 5.1$, 8.1 Hz), 5.15–5.03 (m, 2H, CH_2–Ph), 4.92–4.89 (m, 1H, CH_2–Ph), 4.80–4.76 (m, 2H, –CH_2Ph), 4.68–4.38 (m, 6H, –CH_2Ph, C*H*), 3.81–3.57 (m, 6H, H_2, H_3, H_4, H_5, H_6 and $H_{6'}$), 3.70 (s, 3H, COOMe), 2.97 (dd, 1H, CH_2–COO, $J = 5.1$, 15.7 Hz), 2.75 (dd, 1H, CH_2–COO, $J = 4.7$, 15.7 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$): 171.6, 171.5, 171.0, 138.6, 138.2, 138.1, 137.3, 129.2, 129.1, 129.0, 128.8, 128.7, 128.63, 128.60, 128.4, 128.3, 128.2, 128.1, 128.0, 127.92, 127.89, 82.1, 79.6, 78.6, 77.7, 77.1, 76.6, 75.7, 75.2, 73.7, 72.9, 71.5, 68.5, 67.3, 53.0, 50.9, 38.3; MALDI-TOF-MS: 825.93 ($M+Na^+$), 841.84 ($M+K^+$); IR (Nujol): 3361, 1733, 1716, 1653; $[\alpha]_D^{25} = +37.9$ (*c* 0.5, $CHCl_3$).

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