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Application of bis(diphenylphosphino)ethane (DPPE) in Staudinger-type *N*-glycopyranosyl amide synthesis

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Abstract—Bis(diphenylphosphino)ethane (DPPE) reacts with pyranosyl azides derived from D-glucose and D-glucuronic acid in the presence of acid chlorides to yield the corresponding glycosyl amides. Reaction rates are comparable to those with triphenylphosphine, however, the byproduct phosphine oxide is easily removed from reaction mixtures using column chromatography. The simple and clean workup allows for the formation of collections of related compounds by parallel synthesis, and the method is also applicable to scaled-up reactions. The β-stereochemistry of the glycosyl azide precursor is retained in all cases, which is supported by X-ray crystallography in several cases.

Keywords: *N*-Glycosyl amide; Staudinger reaction; Phosphine; Phosphine oxide

1. Introduction

Amide bonds are used to conjugate carbohydrates to other biomolecules, for example, polypeptides in glycoproteins and nucleic acids, RNA and DNA. The obvious importance of this linkage in biology has driven the search for efficient and stereoselective methodologies for glycosyl amide synthesis.[1] Of major concern in this endeavor is the control of stereochemistry at the anomeric carbon of the saccharide and, with a view to parallel synthesis of novel structures, the development of methods that allow for rapid workup and isolation of products.

N-Glycosyl amides may be prepared by coupling a glycosyl amine with a suitable carboxylic acid derivative; however, problems associated with this method include anomeric interconversion and amine decomposition.[2] The use of Staudinger-type chemistry avoids many of these issues by treating a diastereomerically pure azide precursor with a phosphine and allowing the thus formed phosphinimine ylide to react with a carboxylic acid derivative to give the amide product, usually without loss of the integrity of the anomeric stereochemistry. Unfortunately, many of the phosphines typically employed in the Staudinger-type methods are either inconvenient to work with or give oxide byproducts that are difficult to separate from reaction mixtures.[3–6] Recently the 'Staudinger ligation' process has come to the fore and provides an extremely useful method for conjugating glycosyl azides with peptides to give the naturally occurring β-*N*-glycosyl amide motif.[7–11]

Apart from its occurrence in glycoproteins, the glycosyl amide functionality has received significant attention recently, for example, in the synthesis of multivalent carbohydrate scaffolds,[12,13] as well as for their use as donors in glycosylation reactions.[14,15] Amide-linked glycosyl heterocycles have been reported to possess interesting biological activity,[16–18] therefore the creation of libraries of these compounds would be useful for further biological evaluation, as well as for detailed

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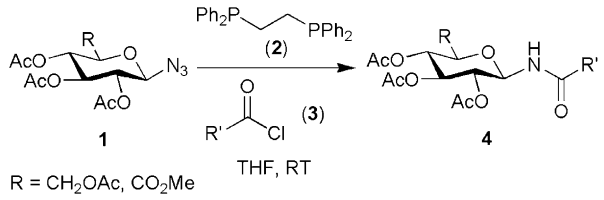


Scheme 1.

structure–activity studies. With a view to the alleviating problems during workup in glycosyl amide library synthesis we have employed polymer-supported triphenylphosphine in Staudinger-type reactions,[19] however, the rates of reaction are much slower with this reagent than with triphenylphosphine itself and the greater cost of the resin-bound phosphine limits its use on scales larger than 1–2 mmol. The readily available bis(diphenylphosphino)ethane (DPPE, **2**, Scheme 1) has been used as a convenient replacement for triphenylphosphine in Mitsunobu and Staudinger reactions,[20] with rates of reaction being similar to those observed with PPh_3, and the byproduct bis(phosphineoxide) is easily removed using simple flash chromatography. Here we describe the reaction of DPPE (**2**) with two β-glycosyl azides (**1**, R = CH_2OAc, CO_2CH_3) in the presence of various acid chlorides (**3**), which affords β-glycosyl amides exclusively (**4**, Scheme 1). The amide products are isolated in very good yields without any contamination from the phosphine oxide byproduct.

2. Results and discussion

2.1. Reaction of DPPE with β-D-glucopyranosyl azide 5

Our initial experiments began with β-glucosyl azide **5** (Scheme 2),[21,22] which was treated with 0.65 equiv of DPPE in the presence of *p*-nitrobenzoyl chloride to give the β-glucosyl amide **6** with complete retention of configuration at the anomeric carbon as judged from ^1H NMR coupling constants and the X-ray structure of **6** (vide infra). Adding DPPE in toluene solution to a THF solution of acid chloride and azide gave the best yield of **6** (92% after workup and column chromatography) and using solvents such as THF or CH_2Cl_2 for dissolution of all reagents gave isolated yields of **6** ranging from 75% to 85%. For library synthesis we relied on slow, dropwise addition of DPPE in THF.

2.2. Structures of the intermediate iminophosphorane ylide and amide products

Evolution of gas (N_2) upon addition of DPPE was consistent with the formation of an iminophosphorane (**7**, Scheme 2), the usual product of such Staudinger reactions.[23–25] Evidence for the dimeric structure of **7** was garnered by adding DPPE to azide **5** in $CDCl_3$ solution and then collecting the ^1H NMR spectrum of the ylide (Fig. 1). Integration of the clearly resolved signal for H-5 of the glucopyranose ring (3.42 ppm) and the broad signal for the [CH_2–CH_2] group (2.51 ppm) was found to be 1:2, which strongly supports the structure for **7** shown in Scheme 2. In the presence of an acid

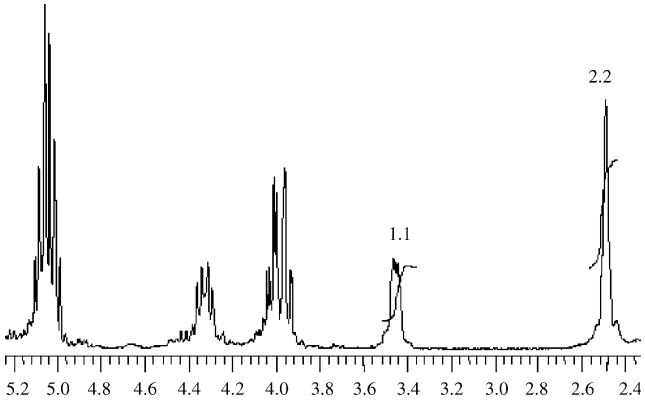
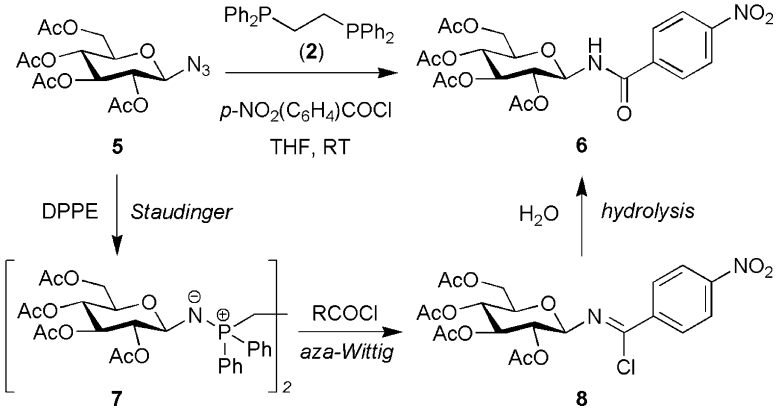


Figure 1. Portion of the ^1H NMR spectrum of ylide **7** collected in $CDCl_3$ solution.



Scheme 2.

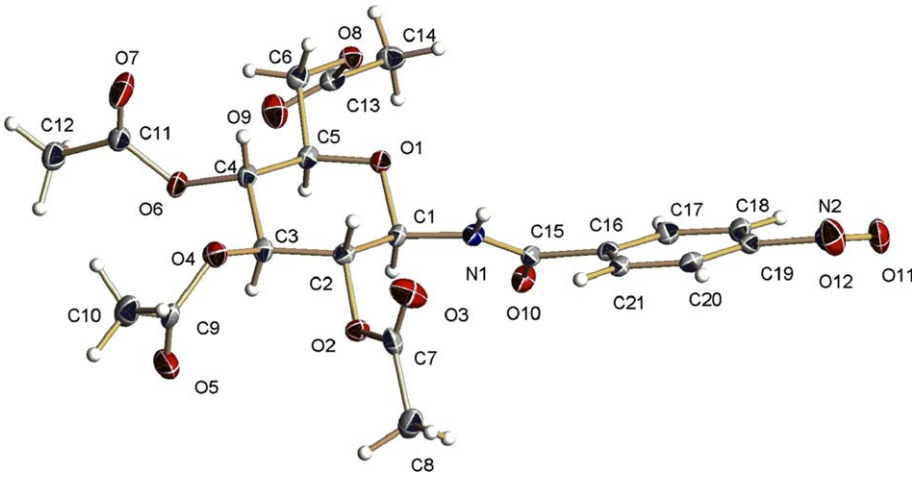


Figure 2. X-ray structure of *N*-glucosyl amide **6** showing 50% probability ellipsoids.

chloride an aza-Wittig reaction ensues (Scheme 2), giving an imidoyl chloride (**8**), which is subsequently hydrolyzed to give the amide product. Amide **6** is readily purified by flash column chromatography and then recrystallized from ethanol.

The structure of glucopyranosyl amide **6** was assigned initially from its ^{1}H, ^{13}C NMR, and mass spectra (*m*/*e* calculated for M^{+}+Na: 519.1227, found: 519.1227) and then supported by its single crystal X-ray structure (Fig. 2, Tables 1 and 2). The ^{1}H NMR spectrum reveals the amide N–H signal as a doublet at 7.30 ppm ($J = 8.8$ Hz) and the signal corresponding to H-1 of the pyranose ring as a triplet (assigned from a COSY experiment) that overlaps with the H-2 signal at 5.4 ppm. Neither the ^{1}H nor ^{13}C NMR spectra show any traces of the (polar) bis-phosphine oxide byproduct.

Table 1. Crystallographic data for *N*-glucopyranosyl amide **6**

Empirical formula	$C_{21}H_{26}N_2O_{13}$
Formula weight	514.44
Crystal size (mm)	$0.39 \times 0.15 \times 0.15$
Crystal system	Orthorhombic
Z	4
Space group	$P2_12_12_1$
a (Å)	6.4411(3), $\alpha = 90°$
b (Å)	17.5338(9), $\beta = 90°$
c (Å)	21.0656(10), $\gamma = 90°$
V (Å^3)	2379.1(2)
Density (calculated) (Mg/m^3)	1.436
$F(000)$	1080
Absorption coefficient (mm^{-1})	0.121
Temperature (K)	100(2)
Wavelength (Å)	0.71073
Crystal shape, color	Block, colorless
θ range for data collection	1.51–28.28°
Limiting indices	$-8 \leqslant h \leqslant 8$, $-23 \leqslant k \leqslant 23$, $-27 \leqslant l \leqslant 28$
Reflections collected	25,550
Independent reflections	5914 (R(int) = 0.0296)
Completeness to $\theta = 28.28°$	100.0%
Absorption correction	Multi-scan
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	5914/0/374
Goodness-of-fit on F^2	1.228
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0457$, $wR_2 = 0.1075$
R indices (all data)	$R_1 = 0.0462$, $wR_2 = 0.1079$
Absolute structure parameter	0.8(7)
Largest diff. peak and hole (eÅ^{-3})	0.341 and −0.286

Table 2. Selected bond lengths (Å) and bond angles (°) for amide **6**

Bond lengths			
C-1–C-2	1.517(3)	C-5–C-6	1.516(3)
C-2–C-3	1.521(3)	C-1–N-1	1.430(3)
C-3–C-4	1.520(3)	C-5–O-1	1.428(3)
C-4–C-5	1.537(3)	C-1–O-1	1.434(3)
Bond angles			
N-1–C-1–O-1	107.30(19)	C-3–C-4–C-5	111.21(19)
N-1–C-1–C-2	110.8(2)	C-4–C-5–C-6	109.4(2)
C-1–C-2–C-3	110.2(2)	O-1–C-5–C-6	106.8(2)
C-2–C-3–C-4	111.31(19)	N-1–C-15–O-10	124.5(2)

The solid state structure of **6** (Fig. 2) clearly shows the N–H amide proton and the C-1 glucopyranosyl ring proton to be aligned in an *anti* fashion. We were interested in correlating this structure with the solution state conformation, which would have obvious ramifications for the spatial presentation of the amide aglycon. The observed C-1–N-1 coupling constant of 8.8 Hz could be reconciled with either *syn* or *anti* alignments around this bond, however, a NOESY experiment revealed interaction between the amide proton and H-2 of the

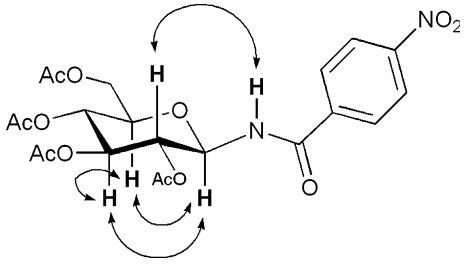


Figure 3. Observed interactions in the NOESY spectrum of **6**.

Table 3. Structures and yields of β-D-glucopyranosyl amides formed from azide **5**

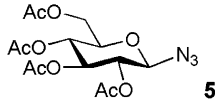
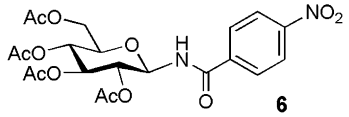
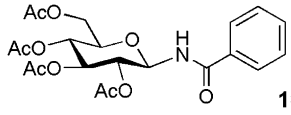
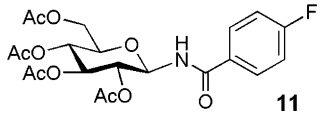
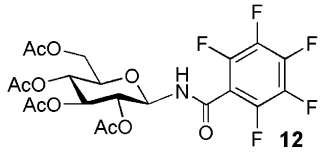
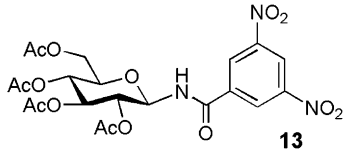
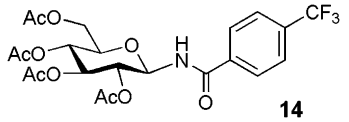
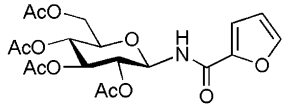
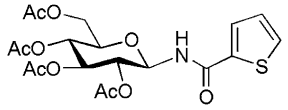
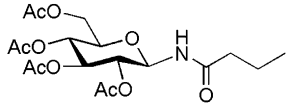
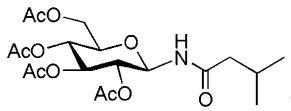
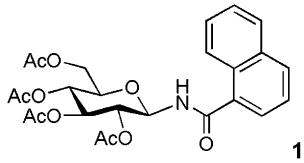
Compound	Yield (%)
 **5**	
 **6**	82
 **10**	60
 **11**	71
 **12**	77
 **13**	58
 **14**	70
 **15**	59
 **16**	75
 **17**	64
 **18**	71
 **19**	50

Table 3 (*continued*)

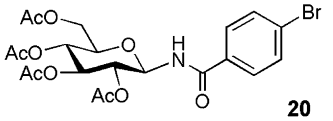
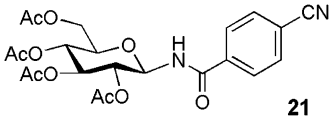
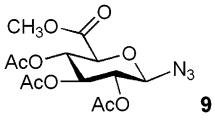
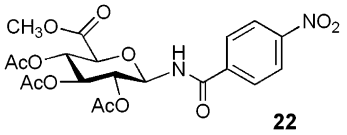
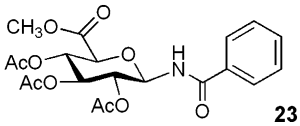
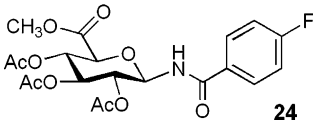
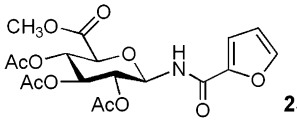
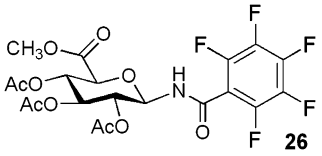
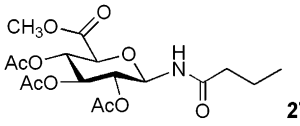
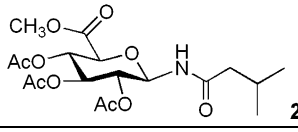
Compound	Yield (%)
 **20**	67
 **21**	74

Table 4. Structures and yields of β-D-glucopyranuronosyl amides formed from azide **9**

Compound	Yield (%)
 **9**	
 **22**	72
 **23**	98
 **24**	80
 **25**	60
 **26**	75
 **27**	70
 **28**	56

glucopyranose ring (as well as between H-1, H-3, and H-5 of the sugar ring) (Fig. 3). The solution conformation about the C-1–N-1 bond in amide **6** is therefore *anti* and is similar to that observed in the solid state (Fig. 2).[26] Both the NMR and X-ray studies reveal that the β-stereochemistry of the azide starting material (**5**) is retained in the amide product and that epimerization is not a significant competing process under the reaction conditions.[27]

2.3. Parallel synthesis of *N*-glycosyl amides

Once the reaction conditions had been optimized for amide **6**, we expanded the synthesis to include the β-glucuronosyl azide **9**[28,29] and studied the reactions of **5** and **9** with a variety of acid chlorides and DPPE (Tables 3 and 4). Using a simple parallel synthesizer we were able to run multiple reactions in series and, after an aqueous workup, the amides were isolated by flash column chromatography. In all cases the β-glycosyl amides were isolated in good yields in >95% purity (NMR) without any contamination from the bis-phosphine oxide byproduct.

All of the *N*-glycopyranosyl amides formed here gave satisfactory NMR spectral and mass spectral data in accordance with their assigned structures and further support for the β-selectivity was obtained from the X-ray crystal structure of the thiophene derivative **16** (Fig. 4, Tables 5 and 6). The *anti* conformation about the C-1–N-1 bond can clearly be seen, as can the retention of the chair conformation within the pyranose ring.

Table 5. Crystallographic data for *N*-glucopyranosyl amide **16**

Empirical formula	$C_{19}H_{23}NO_{10}S$
Formula weight	457.44
Crystal size (mm)	$0.44 \times 0.39 \times 0.36$
Crystal system	Monoclinic
Z	4
Space group	$C2$
a (Å)	16.247(3), $\alpha = 90°$
b (Å)	14.105(3), $\beta = 124.950(3)°$
c (Å)	11.182(2), $\gamma = 90°$
V (Å^3)	2100.4(7)
Density (calculated) (Mg/m^3)	1.447
$F(000)$	960
Absorption coefficient (mm^{-1})	0.211
Temperature (K)	100(2)
Wavelength (Å)	0.71073
Crystal shape, color	Block, colorless
θ range for data collection	2.10–30.50°
Limiting indices	$-22 \leqslant h \leqslant 23, -20 \leqslant k \leqslant 20, -15 \leqslant l \leqslant 15$
Reflections collected	12,648
Independent reflections	6292 (R(int) = 0.0157)
Completeness to $\theta = 30.50°$	99.9%
Absorption correction	Multi-scan
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	6292/1/284
Goodness-of-fit on F^2	1.034
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0322$, $wR_2 = 0.0848$
R indices (all data)	$R_1 = 0.0326$, $wR_2 = 0.0852$
Absolute structure parameter	−0.01(4)
Largest diff. peak and hole (eÅ^{-3})	0.413 and −0.292

2.4. Mechanism of amide formation

While most of the glycosyl amides in Tables 3 and 4 were formed readily, albeit at different rates, the reactions to give the furan derivatives **15** and **25** (Tables 3 and 4) were notably slower than in other cases. Indeed, in the case of azide **5**, working the reaction up after 1 h did not afford amide **15** but a compound considered to be the imidoyl chloride **30** (Scheme 3), which is the putative intermediate formed during the aza-Wittig portion of the conversion of azide **5** to the amide. This compound was stable to column chromatography, crystallized upon isolation (68% yield), and was amenable to

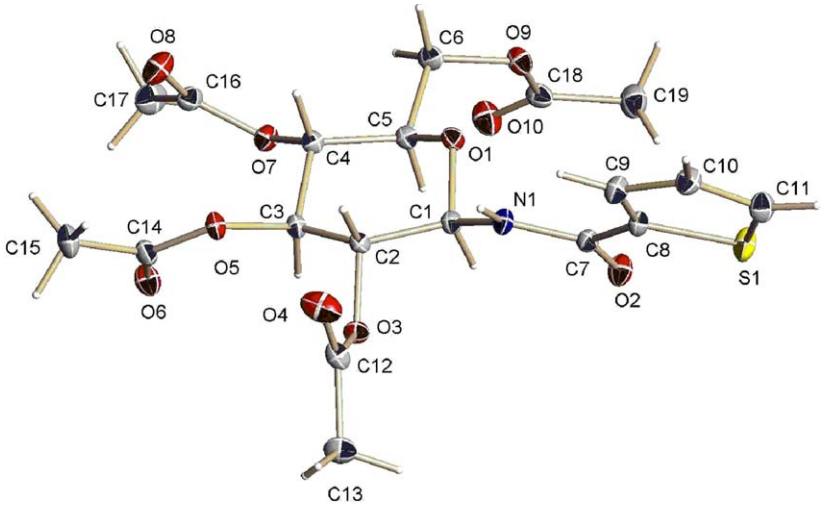


Figure 4. X-ray structure of *N*-glycosyl amide **16** showing 50% probability ellipsoids.

Table 6. Selected bond lengths (Å) and bond angles (°) for amide **16**

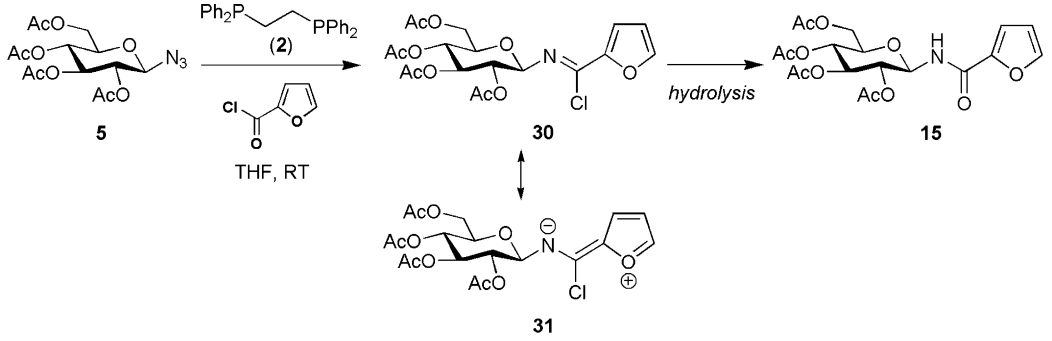
Bond lengths			
C-1–C-2	1.5236(15)	C-5–C-6	1.5102(15)
C-2–C-3	1.5286(15)	C-1–N-1	1.4322(14)
C-3–C-4	1.5288(15)	C-5–O-1	1.4366(13)
C-4–C-5	1.5248(15)	C-1–O-1	1.4403(12)
Bond angles			
N-1–C-1–O-1	108.14(8)	C-3–C-4–C-5	108.10(8)
N-1–C-1–C-2	110.04(9)	C-4–C-5–C-6	109.4(2)
C-1–C-2–C-3	113.88(9)	O-1–C-5–C-6	108.09(9)
C-2–C-3–C-4	112.16(8)	N-1–C-7–O-2	122.50(10)

analysis by NMR and mass spectrometry, data that agreed with the structure assigned to **30** (*m*/*z* for M^++Na calculated; 482.0830, found; 482.0835). The low rate of hydrolysis of this material is likely explained by stabilization of the imidoyl carbonyl by donation of electron density from the furan ring (resonance structure **31** in Scheme 3). Even under basic conditions the chloride was sluggish in converting to the amide; in fact deacetylation of the sugar protecting groups became a competitive process.

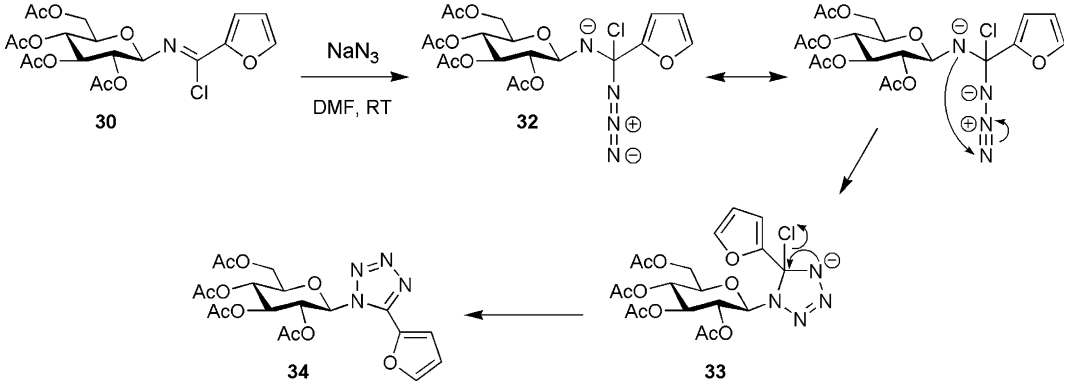
While spectroscopic evidence pointed to the imidoyl chloride **30** we wished to prove this chemically and thus treated this material with NaN_3 in DMF in an effort to displace the chloride ion with a powerful nucleophile. After stirring at rt for 5 h the imidoyl chloride was consumed and the workup yielded a syrupy product in 95% yield that proved to be the 5-substituted glycosyl tetrazole **34** (Scheme 4). The formation of **34** may be explained by nucleophilic attack of azide at the imidoyl carbonyl, to produce tetrahedral intermediate **32**, which then undergoes a 5-endo-trig cyclization to give **33**, which in turn loses chloride to afford the aromatic tetrazole product. Synthesis of 1,5-disubstituted tetrazoles by combining imidoyl chlorides with sodium azide is known from the literature,[30] however, **34** appears to be the first example of this type of compound involving a carbohydrate.

3. Conclusions

We have shown that using bis(diphenylphosphino)-ethane (DPPE) in place of PPh_3 in the Staudinger-type synthesis of glucosyl and glucuronosyl amides removes some of the drawbacks associated with the removal of triphenylphoshine oxide from reaction mixtures. The polar bis-phosphine oxide is readily separated from amide products, which allows for the convenient synthesis of collections of related glycosyl amides. The evidence gained from NMR and X-ray crystallography



Scheme 3.



Scheme 4.

shows that the amides adopt an *anti* conformation about the C-1–N-1 bond, and that the β-configuration of the azide precursor is retained in the amide product. Isolation of the imidoyl chloride intermediate (**30**) from reaction with 2-furoyl chloride provides an indication of the mechanism operating in the Staudinger–aza-Wittig sequence, and the formation of a 5-substituted glucosyl tetrazole (**34**) from this imidoyl chloride opens an avenue for further exploration.

4. Experimental

4.1. General methods

Reactions were monitored by TLC using pre-coated aluminum-backed plates and compounds were visualized using a 5% H_2SO_4 in EtOH solution with subsequent burning. All samples described here were recrystallized from EtOH and are homogeneous by TLC. NMR spectra were recorded on a Varian Gemini 2000 system at 400 MHz for ^1H and 100 MHz for ^{13}C. Low resolution mass spectra (LRMS) were collected using a Bruker Esquire-HP 1100 instrument at YSU and high resolution spectra (ESIMS) were collected on a Micromass LCT instrument at The Ohio State University Campus Chemical Instrumentation Center. Optical rotations were determined on a Perkin–Elmer 343 automatic polarimeter as solutions in CH_2Cl_2. Diffraction data of compounds **6** and **16** were collected on a Bruker AXS SMART APEX CCD diffractometer at 100(2) K using monochromatic Mo Kα radiation with omega scan technique using the SMART software.[31] The unit cell was determined using SAINT+.[32] The structure was solved by direct methods and refined by full matrix least squares against F^2 with all reflections using SHELXTL.[33] Refinement of an extinction coefficient was found to be insignificant. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed in calculated positions and refined with an isotropic displacement parameter 1.5 (CH_3) or 1.2 times (all others) that of the adjacent carbon or nitrogen atom. CCDC-294740 (**6**) and CCDC-294741 (**16**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 (0)1223 336033.

4.2. General procedure for glucosyl and glucuronosyl amide synthesis

The azide (**5** or **9**, 1.0 mmol) and acid chloride (2.0 mmol) were dissolved in dry THF (0.1 g/mL) and bis(diphenylphosphino)ethane (**2**, 0.65 mmol) in THF (0.1 g/mL) was added dropwise at rt. The mixture was allowed to stir until TLC showed reaction to be complete (disappearance of the intermediate ylide). A saturated $NaHCO_3$ solution (2 mL) was added and the mixture stirred vigorously for 3 h. The organic solvent was removed under reduced pressure and the residue was partitioned between $CHCl_3$ (20 mL) and water (20 mL). The aqueous layer was extracted with further portions of $CHCl_3$ (2×20 mL) and the combined organic extracts were washed with water (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product was isolated by flash column chromatography using the appropriate eluent.

4.3. 4-Nitro-*N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)benzamide (6)

Colorless solid (0.405 g, 82%) isolated from flash column chromatography using 1:1 hexane/EtOAc: mp 199–201 °C, lit.[5] 168–170 °C; $[\alpha]_D$ −29.6 (*c* 1.0, CH_2Cl_2), lit.[5] −16.5; ^1H NMR ($CDCl_3$) δ 2.06 (s, 6H, $2 \times COCH_3$), 2.07 (s, 3H, $COCH_3$), 2.09 (s, 3H, $COCH_3$), 3.93 (ddd, 1H, $J = 2.1$, 4.2, 10.1 Hz, H-5), 4.12 (dd, 1H, $J = 2.1$, 12.5 Hz, H-6), 4.33 (dd, 1H, $J = 4.3$, 12.5 Hz, H-6′), 5.05 (t, 1H, $J = 9.6$ Hz, H-3), 5.12 (t, 1H, $J = 9.8$ Hz, H-4), 5.42 ($2 \times$ t, overlapping, 2H, $J = 9.5$, 9.2 Hz, H-1, H-2), 7.29 (d, 1H, $J = 8.8$ Hz, N–H), 7.95 (d, 2H, $J = 9.2$ Hz, Ar–H), 8.32 (d, 2H, $J = 8.8$ Hz, Ar–H); ^{13}C NMR ($CDCl_3$) δ 20.7 ($2 \times C$), 20.81, 20.84, 61.6, 68.1, 70.9, 72.3, 73.7, 79.0, 123.8 ($2 \times C$), 128.4 ($2 \times C$), 138.0, 149.9, 164.9, 169.3, 169.6, 170.3, 171.5; ESIMS calcd for $C_{21}H_{24}N_2O_{12}$: 519.1227 (+Na), found: 519.1227 (+Na). The X-ray crystal structure of this compound is discussed in the text.

4.4. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-benzamide (10)

Colorless solid (0.406 g, 60%) isolated from flash column chromatography using 1:1 hexane/EtOAc: mp 190–192 °C; $[\alpha]_D$ −14.5 (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 2.05 (s, 3H, $COCH_3$), 2.06 (s, 6H, $2 \times COCH_3$), 2.08 (s, 3H, $COCH_3$), 3.92 (ddd, 1H, $J = 2.1$, 4.2, 10.2 Hz, H-5), 4.10 (dd, 1H, $J = 2.1$, 12.5 Hz, H-6), 4.36 (dd, 1H, $J = 4.2$, 12.6 Hz, H-6′), 5.08 (t, 1H, $J = 9.6$ Hz, H-3), 5.12 (t, 1H, $J = 9.7$ Hz, H-4), 5.40 (t, 1H, $J = 9.5$ Hz, H-2), 5.46 (t, 1H, $J = 9.3$ Hz, H-1), 7.14 (d, 1H, $J = 9.2$ Hz, N–H), 7.43–7.47 (m, 2H, Ar–H), 7.53 (m, 1H, Ar–H), 7.76–7.78 (m, 2H, Ar–H); ^{13}C NMR ($CDCl_3$): δ 20.7 ($2 \times C$), 20.8 ($2 \times C$), 61.6, 68.1, 70.7, 72.5, 73.5, 78.8, 127.0, 128.6 ($3 \times C$), 132.2, 132.5, 166.8, 169.3, 169.6, 170.4, 171.2; ESIMS calcd for $C_{21}H_{25}NO_{10}$: 474.1376 (+Na), found: 474.1337 (+Na). This data is in agreement with a sample of **10** produced previously by a different method.[12]

4.5. 4-Fluoro-*N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)benzamide (11)

Colorless solid (0.331 g, 71%) isolated from flash column chromatography using 1:1 hexane/EtOAc: mp 149–152 °C; $[\alpha]_D$ −17.8 (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 2.05 (s, 9H, $3\times COCH_3$), 2.08 (s, 3H, $COCH_3$), 3.91 (ddd, 1H, $J = 2.1$, 4.2, 10.2 Hz, H-5), 4.11 (dd, 1H, $J = 2.0$, 12.6 Hz, H-6), 4.36 (dd, 1H, $J = 4.2$, 12.6 Hz, H-6′), 5.05 (t, 1H, $J = 9.7$ Hz, H-2), 5.12 (t, 1H, $J = 9.7$ Hz, H-3), 5.40 (t, 1H, $J = 9.6$ Hz, H-4), 5.41 (t, 1H, $J = 9.3$ Hz, H-1), 7.03 (d, 1H, $J = 9.0$ Hz, N–H), 7.11–7.15 (m, 2H, Ar–H), 7.76–7.80 (m, 2H, Ar–H); ^{13}C NMR ($CDCl_3$): δ 20.6 (2 × C), 20.8 (2 × C), 61.6, 68.1, 70.8, 72.5, 73.5, 78.8, 115.7 (2 × C, d, $J = 22.1$ Hz), 128.7 (d, $J = 3.1$ Hz), 129.54 (2 × C, d, $J = 9.2$ Hz), 164.9 (d, $J = 252.5$ Hz), 165.8, 169.3, 169.5, 170.3, 171.2; LRMS calcd for $C_{21}H_{24}FNO_{10}$: 492.128 (+Na), found: 492.2 (+Na).

4.6. 2,3,4,5,6-Pentafluoro-*N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)benzamide (12)

Colorless solid (0.418 g, 77%) isolated from flash column chromatography using 7:4 hexane/EtOAc: mp 129–132 °C; $[\alpha]_D$ +4.7 (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 2.04 (s, 3H, $COCH_3$), 2.05 (s, 3H, $COCH_3$), 2.09 (s, 3H, $COCH_3$), 2.10 (s, 3H, $COCH_3$), 3.90 (ddd, 1H, $J = 2.1$, 4.3, 10.2 Hz, H-5), 4.12 (dd, 1H, $J = 2.2$, 12.5 Hz, H-6), 4.36 (dd, 1H, $J = 4.5$, 12.5 Hz, H-6′), 5.02 (t, 1H, $J = 9.6$ Hz, H-3), 5.10 (t, 1H, $J = 9.7$ Hz, H-4), 5.36 (t, 1H, $J = 9.5$ Hz, H-2), 5.39 (t, 1H, $J = 9.3$ Hz, H-1), 6.95 (d, 1H, $J = 9.2$ Hz, N–H); ^{13}C NMR ($CDCl_3$): δ 20.6, 20.7 (2 × C), 20.8, 61.5, 68.0, 70.2, 72.4, 73.9, 78.4, 110.2, 137.4 (2 × C, d, $J = 256.4$ Hz), 142.5 (d, $J = 258.6$ Hz), 143.9 (2 × C, d, $J = 248.7$ Hz), 157.6, 169.3, 169.6, 170.4, 170.8; ESIMS calcd for $C_{21}H_{20}F_5NO_{10}$: 564.0905 (+Na), found: 564.0915 (+Na).

4.7. 3,5-Dinitro-*N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)benzamide (13)

Colorless solid (0.283 g, 58%) isolated from flash column chromatography using 5:4 hexane/EtOAc: mp 149–152 °C; $[\alpha]_D$ −36.8 (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 2.07 (s, 6H, $2\times COCH_3$), 2.08 (s, 3H, $COCH_3$), 2.09 (s, 3H, $COCH_3$), 3.94 (ddd, 1H, $J = 2.2$, 4.5, 10.2 Hz, H-5), 4.14 (dd, 1H, $J = 2.1$, 12.5 Hz, H-6), 4.34 (dd, 1H, $J = 4.4$, 12.6 Hz, H-6′), 5.07 (t, 1H, $J = 9.6$ Hz, H-2), 5.14 (t, 1H, $J = 9.8$ Hz, H-3), 5.43 (t, 1H, $J = 9.6$ Hz, H-4), 5.45 (t, 1H, $J = 9.52$ Hz, H-1), 7.64 (d, 1H, $J = 8.6$ Hz, N–H), 8.98 (d, 2H, $J = 2.2$ Hz, Ar–H), 9.21 (t, 1H, $J = 2.0$ Hz, Ar–H); ^{13}C NMR ($CDCl_3$): δ 20.6, 20.7, 20.8 (2 × C), 61.9, 68.2, 70.9, 72.5, 73.8, 78.8, 121.6, 127.5, 136.1, 148.5 ($2\times CH_3$), 162.6, 169.6 (2 × C), 170.5, 171.1; ESIMS calcd for $C_{21}H_{23}N_3O_{14}$: 564.1078 (+Na), found: 564.1074 (+Na).

4.8. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-4-trifluoromethylbenzamide (14)

Colorless solid (0.364 g, 70%) isolated from flash column chromatography using 1:1 hexane/EtOAc: mp 189–190 °C; $[\alpha]_D$ −15.7 (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 2.06 (s, 9H, $3\times COCH_3$), 2.08 (s, 3H, $COCH_3$), 3.93 (ddd, 1H, $J = 2.1$, 4.2, 10.2 Hz, H-5), 4.12 (dd, 1H, $J = 2.0$, 12.6 Hz, H-6), 4.36 (dd, 1H, $J = 4.3$, 12.5 Hz, H-6′), 5.07 (t, 1H, $J = 9.6$ Hz, H-2), 5.12 (t, 1H, $J = 9.8$ Hz, H-3), 5.42 (t, 1H, $J = 9.5$ Hz, H-4), 5.45 (t, 1H, $J = 9.3$ Hz, H-1), 7.29 (d, 1H, $J = 8.8$ Hz, N–H), 7.72 (d, 2H, $J = 8.4$ Hz, Ar–H), 7.89 (d, 2H, $J = 8.1$ Hz, Ar–H); ^{13}C NMR ($CDCl_3$): δ 20.6 (2 × C), 20.8 (2 × C), 61.6, 68.1, 70.8, 72.4, 73.6, 78.9, 123.3 (q, $J = 271.9$ Hz), 125.6 (2 × C, q, $J = 3.1$ Hz), 127.6, 133.9 (2 × C, q, $J = 32.8$ Hz), 135.8, 165.6, 169.3, 169.5, 170.3, 171.3; LRMS calcd for $C_{22}H_{24}F_3NO_{10}$: 542.125 (+Na), found: 542.2 (+Na).

4.9. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)furan-2-carboxamide (15)

Colorless solid (0.26 g, 59%) isolated from flash column chromatography using 4:5 hexane/EtOAc: mp 160–163 °C; $[\alpha]_D$ −17.7 (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 2.03 (s, 3H, $COCH_3$), 2.04 (s, 3H, $COCH_3$), 2.05 (s, 3H, $COCH_3$), 2.08 (s, 3H, $COCH_3$), 3.90 (ddd, 1H, $J = 2.1$, 4.3, 10.2 Hz, H-5), 4.10 (dd, 1H, $J = 2.1$, 12.5 Hz, H-6), 4.38 (dd, 1H, $J = 4.3$, 12.5 Hz, H-6′), 5.08 (t, 1H, $J = 9.6$ Hz, H-3), 5.12 (t, 1H, $J = 9.7$ Hz, H-4), 5.38, 5.43 (2t overlapping, 2H, $J = 9.9$, 9.5 Hz, H-1, H-2), 6.52 (dd, 1H, $J = 1.8$, 3.5 Hz, Ar–H), 7.16 (d, 1H, $J = 9.3$ Hz, N–H), 7.18 (d, 1H, $J = 3.5$ Hz, Ar–H), 7.50 (d, 1H, $J = 1.8$ Hz, Ar–H); ^{13}C NMR ($CDCl_3$): δ 20.6 (2 × C), 20.7, 20.8, 61.5, 68.0, 70.3, 72.6, 73.4, 77.9, 112.2, 115.8, 144.7, 146.3, 157.8, 169.3, 169.6, 170.3, 170.6; ESIMS calcd for $C_{19}H_{23}NO_{11}$: 464.1169 (+Na), found: 464.1169 (+Na).

4.10. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)thiophene-2-carboxamide (16)

Colorless solid (0.342 g, 75%) isolated from flash column chromatography using 3:2 hexane/EtOAc: mp 170–171 °C; $[\alpha]_D$ −32.2 (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 2.04 (s, 3H, $COCH_3$), 2.05 (2s overlapping, 6H, $COCH_3$), 2.09 (s, 3H, $COCH_3$), 3.90 (ddd, 1H, $J = 2.1$, 4.3, 10.2 Hz, H-5), 4.11 (dd, 1H, $J = 2.1$, 12.5 Hz, H-6), 4.36 (dd, 1H, $J = 4.3$, 12.5 Hz, H-6′), 5.04 (t, 1H, $J = 9.6$ Hz, H-3), 5.11 (t, 1H, $J = 9.8$ Hz,

H-4), 5.38 (t, 1H, $J = 9.3$ Hz, H-2), 5.39 (t, 1H, $J = 9.5$ Hz, H-1), 6.94 (d, 1H, $J = 9.0$ Hz, N–H), 7.09 (dd, 1H, $J = 3.8$, 5.0 Hz, Ar–H), 7.49 (dd, 1H, $J = 1.1$, 3.9 Hz, Ar–H), 7.55 (dd, 1H, $J = 1.1$, 5.1 Hz, Ar–H); ^{13}C NMR ($CDCl_3$): δ 20.7 (2 × C), 20.8 (2 × C), 61.6, 68.1, 70.6, 72.5, 73.5, 78.8, 127.2, 129.0, 131.5, 137.3, 161.4, 169.3, 169.6, 170.4, 171.3; ESIMS calcd for $C_{19}H_{23}NO_{10}S$: 480.0940 (+Na), found: 480.0936 (+Na). Only mass spectral data for this compound has been reported previously.[18]

4.11. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-butyramide (17)

Colorless solid (0.273 g, 64%) isolated from flash column chromatography using 3:2 hexane/EtOAc: mp 114–117 °C; $[\alpha]_D$ +12.9 (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 0.92 (t, 3H, $J = 7.42$ Hz, H_γ), 1.58 (m, 2H, H_β), 2.10 (m, 2H, H_α), 2.03 (s, 3H, $COCH_3$), 2.04 (s, 3H, $COCH_3$), 2.05 (s, 3H, $COCH_3$), 2.09 (s, 3H, $COCH_3$), 3.85 (ddd, 1H, $J = 2.1$, 4.3, 10.2 Hz, H-5), 4.08 (dd, 1H, $J = 2.1$, 12.5 Hz, H-6), 4.33 (dd, 1H, $J = 4.3$, 12.5 Hz, H-6′), 4.94 (t, 1H, $J = 9.6$ Hz, H-2), 5.07 (t, 1H, $J = 9.7$ Hz, H-4), 5.30 (t, 1H, $J = 9.7$ Hz, H-1), 5.32 (t, 1H, $J = 9.6$ Hz, H-3), 6.44 (d, 1H, $J = 9.3$ Hz, N–H); ^{13}C NMR ($CDCl_3$): δ 13.6, 18.6, 20.59 (2 × C), 20.64, 20.7, 38.4, 61.6, 68.0, 70.4, 72.6, 73.4, 77.9, 169.2, 169.5, 170.3, 170.5, 172.9; ESIMS calcd for $C_{18}H_{27}NO_{10}$: 440.1533 (+Na), found: 440.1541 (+Na).

4.12. 3-Methyl-*N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)butanamide (18)

Colorless solid (0.303 g, 71%) isolated from flash column chromatography using 1:2 hexane/EtOAc: mp 137–139 °C; $[\alpha]_D$ +11.8 (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 0.91 (d, 3H, $J = 6.2$ Hz, H_γ), 0.94 (d, 3H, $J = 6.2$ Hz, H_γ), 1.96–2.15 (m, 3H, H_α, H_β), 2.03 (s, 3H, $COCH_3$), 2.04 (s, 6H, 2 × $COCH_3$), 2.08 (s, 3H, $COCH_3$), 3.83 (ddd, 1H, $J = 2.1$, 4.4, 10.1 Hz, H-5), 4.07 (dd, 1H, $J = 2.1$, 12.5 Hz, H-6), 4.33 (dd, 1H, $J = 4.4$, 12.5 Hz, H-6′), 4.93 (t, 1H, $J = 9.6$ Hz, H-3), 5.07 (t, 1H, $J = 9.8$ Hz, H-4), 5.28 (t, 1H, $J = 9.5$ Hz, H-2), 5.31 (t, 1H, $J = 9.5$ Hz, H-1), 6.22 (d, 1H, $J = 9.3$ Hz, N–H); ^{13}C NMR ($CDCl_3$): δ 20.6 (2 × C), 20.7, 20.8, 22.2, 22.3, 26.0, 45.9, 61.6, 68.1, 70.4, 72.6, 73.4, 77.9, 169.2, 169.5, 170.3, 170.6, 172.5; ESIMS calcd for $C_{19}H_{29}NO_{10}$: 454.1689 (+Na), found: 454.1691 (+Na).

4.13. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1-naphthamide (19)

Colorless solid (0.25 g, 50%) isolated from flash column chromatography using 1:1 hexane/EtOAc: mp 165–168 °C, lit.[6] 138–140 °C; $[\alpha]_D$ +16.5 (*c* 1.0, CH_2Cl_2), lit.[6] +38.0 (*c* 0.21, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.05 (s, 3H, $COCH_3$), 2.06 (s, 3H, $COCH_3$), 2.09 (s, 3H, $COCH_3$), 2.10 (s, 3H, $COCH_3$), 3.95 (ddd, 1H, $J = 2.1$, 4.2, 10.1 Hz, H-5), 4.16 (dd, 1H, $J = 2.1$, 12.5 Hz, H-6), 4.37 (dd, 1H, $J = 4.3$, 12.5 Hz, H-6′), 5.06 (t, 1H, $J = 9.6$ Hz, H-2), 5.13 (t, 1H, $J = 9.7$ Hz, H-3), 5.41 (t, 1H, $J = 9.5$ Hz, H-4), 5.58 (t, 1H, $J = 9.4$ Hz, H-1), 6.83 (d, 1H, $J = 9.7$ Hz, N–H), 7.45 (dd, 1H, $J = 7.1$, 8.1 Hz, Ar–H), 7.51–7.58 (m, 2H, Ar–H), 7.86–7.89 (m, 1H, Ar–H), 7.95 (d, 1H, $J = 8.2$ Hz, Ar–H,), 8.32–8.35 (m, 1H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 20.7 (2 × C), 20.78, 20.83, 61.7, 68.2, 70.7, 72.8, 73.7, 78.4, 124.4, 125.0, 125.1, 126.4, 127.2, 128.2, 129.9, 131.5, 132.1, 133.5, 169.0, 169.3, 169.6, 170.4, 170.7; LRMS calcd for $C_{25}H_{27}NO_{10}$: 524.153 (+Na), found: 524.2 (+Na).

4.14. 4-Bromo-*N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)benzamide (20)

Colorless solid (0.36 g, 67%) isolated from flash column chromatography using 1:1 hexane/EtOAc: mp 179–180 °C; $[\alpha]_D$ −2.6 (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 2.05 (s, 3H, $COCH_3$), 2.06 (s, 6H, 2 × $COCH_3$), 2.08 (s, 3H, $COCH_3$), 3.91 (ddd, 1H, $J = 2.0$, 4.1, 10.1 Hz, H-5), 4.11 (dd, 1H, $J = 2.1$, 12.5 Hz, H-6), 4.36 (dd, 1H, $J = 4.2$, 12.6 Hz, H-6′), 5.04 (t, 1H, $J = 9.6$ Hz, H-2), 5.12 (dd, 1H, $J = 9.7$ Hz, H-3), 5.40 (t, 1H, $J = 9.6$ Hz, H-4), 5.41 (t, 1H, $J = 9.3$ Hz, H-1), 7.04 (d, 1H, $J = 9.0$ Hz, N–H), 7.58–7.64 (m, 4H, Ar–H); ^{13}C NMR ($CDCl_3$): δ 20.6 (2 × C), 20.7 (2 × C), 61.5, 68.1, 70.7, 72.4, 73.5, 78.8, 127.1, 128.6, 131.4, 131.7, 165.9, 169.3, 169.5, 170.2, 171.1; LRMS calcd for $C_{21}H_{24}BrNO_{10}$: 552.048 (+Na), found: 552.2 (+Na).

4.15. 4-Cyano-*N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)benzamide (21)

Colorless solid (0.352 g, 74%) isolated from flash column chromatography using 1:1 hexane/EtOAc: mp 105–107 °C; $[\alpha]_D$ −22.3 (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 2.06 (s, 9H, 3 × $COCH_3$), 2.08 (s, 3H, $COCH_3$), 3.92 (ddd, 1H, $J = 2.1$, 4.3, 10.1 Hz, H-5), 4.12 (dd, 1H, $J = 4.3$, 12.5 Hz, H-6), 4.35 (dd, 1H, $J = 2.1$, 12.5 Hz, H-6′), 5.04 (t, 1H, $J = 9.6$ Hz, H-2), 5.12 (t, 1H, $J = 9.8$ Hz, H-3), 5.41 (2 × t, overlapping, 2H, $J = 9.2$, 9.5 Hz, H-1, H-4), 7.27 (d, 1H, $J = 8.4$ Hz, N–H), 7.76 (m, 2H, Ar–H), 7.86 (m, 2H, Ar–H); ^{13}C NMR ($CDCl_3$): δ 21.9 (2 × C), 22.0, 22.1, 62.7, 69.2, 72.0, 73.5, 74.8, 80.1, 117.1, 118.9, 129.0, 133.7, 137.6, 166.4, 170.6, 170.9, 171.6, 172.9; LRMS calcd for $C_{22}H_{24}N_2O_{10}$: 499.133 (+Na), found: 499.2 (+Na).

4.16. *N*-(Methyl 2,3,4-tetra-*O*-acetyl-β-D-glucuronosyl)-4-nitro-benzamide (22)

Colorless solid (0.347 g, 72%) isolated from flash column chromatography using 1:1 hexane/EtOAc: mp 105–107 °C; $[\alpha]_D$ −49.7 (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 2.05 (s, 6H, $2\times COCH_3$), 2.06 (s, 3H, $COCH_3$), 3.72 (s, 3H, $-OCH_3$), 4.25 (d, 1H, $J = 9.9$ Hz, H-5), 5.05 (t, 1H, $J = 9.6$ Hz, H-4), 5.16 (t, 1H, $J = 9.7$ Hz, H-2), 5.37 (t, 1H, $J = 9.8$ Hz, H-3), 5.47 (t, 1H, $J = 9.1$ Hz, H-1), 7.39 (d, 1H, $J = 9.0$ Hz, N–H), 7.93 (d, 2H, $J = 8.6$ Hz, Ar–H), 8.30 (d, 2H, $J = 8.4$ Hz, Ar–H); ^{13}C NMR ($CDCl_3$): δ 21.6, 21.7, 21.8, 54.0, 70.5, 71.6, 72.9, 74.5, 79.4, 124.7 ($2\times C$), 129.8 ($2\times C$), 139.1, 150.8, 166.6, 168.1, 170.5, 170.7, 171.8; ESIMS calcd for $C_{20}H_{22}N_2O_{12}$: 505.1070 (+Na), found: 505.1056 (+Na).

4.17. *N*-(Methyl 2,3,4-tetra-*O*-acetyl-β-D-glucuronosyl)-benzamide (23)

Colorless solid (0.428 g, 98%) isolated from flash column chromatography using 2:1 hexane/EtOAc: mp 193–195 °C; $[\alpha]_D$ −19.1 (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 2.04 (s, 3H, $COCH_3$), 2.05 (s, 3H, $COCH_3$), 2.06 (s, 3H, $COCH_3$), 3.72 (s, 3H, $-OCH_3$), 4.24 (d, 1H, $J = 10.1$ Hz, H-5), 5.10 (t, 1H, $J = 9.6$ Hz, H-4), 5.18 (t, 1H, $J = 10.1$ Hz, H-2), 5.47 (t, 1H, $J = 9.6$ Hz, H-3), 5.48 (t, 1H, $J = 9.2$ Hz, H-1), 7.15 (d, 1H, $J = 9.2$ Hz, N–H), 7.44 (t, 2H, $J = 6.6$ Hz, Ar–H), 7.53 (t, 1H, $J = 7.1$ Hz, Ar–H), 7.75 (d, 2H, $J = 6.8$ Hz, Ar–H); ^{13}C NMR ($CDCl_3$): δ 21.7, 21.8, 21.9, 54.0, 70.8, 71.7, 73.0, 74.9, 79.6, 128.3 ($2\times C$), 129.7 ($2\times C$), 133.4, 133.7, 168.1, 168.2, 170.4, 170.7, 172.1; ESIMS calcd for $C_{20}H_{23}NO_{10}$: 460.1220 (+Na), found: 460.1221 (+Na). The deacetylated derivative of this compound has been reported.[18]

4.18. 4-Fluoro-*N*-(methyl 2,3,4-tetra-*O*-acetyl-β-D-glucuronosyl)benzamide (24)

Colorless solid (0.364 g, 80%) isolated from flash column chromatography using 1:1 hexane/EtOAc: mp 116–119 °C; $[\alpha]_D$ −31.3 (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 2.00 (s, 3H, $COCH_3$), 2.03 (s, 6H, $2\times COCH_3$), 3.66 (s, 3H, $-OCH_3$), 4.24 (d, 1H, $J = 10.1$ Hz, H-5), 5.09 (t, 1H, $J = 9.5$ Hz, H-4), 5.12 (t, 1H, $J = 9.5$ Hz, H-2), 5.46 (t, 1H, $J = 9.5$ Hz, H-3), 5.50 (t, 1H, $J = 9.2$ Hz, H-1), 7.06 (dd, 2H, $J = 8.5$, 8.5 Hz, Ar–H), 7.40 (d, 1H, $J = 9.2$ Hz, N–H), 7.76 (dd, 2H, $J = 8.5$, 4.7 Hz, Ar–H); ^{13}C NMR ($CDCl_3$): δ 21.7, 21.8, 21.9, 54.0, 70.8, 71.7, 73.0, 74.8, 79.6, 116.6 (d, $2\times C$, $J = 22.1$ Hz), 129.9, 130.9 (d, $2\times C$, $J = 9.2$ Hz), 164.8, 166.1 (d, $J = 252.5$ Hz), 167.3, 168.2, 170.9, 172.6; ESIMS calcd for $C_{20}H_{22}FNO_{10}$: 478.1125 (+Na), found: 478.1133 (+Na).

4.19. *N*-(Methyl 2,3,4-tetra-*O*-acetyl-β-D-glucuronosyl)-furan-2-carboxamide (25)

Colorless solid (0.256 g, 60%) isolated from flash column chromatography using 1:1 hexane/EtOAc: mp 137–140 °C; $[\alpha]_D$ +36.0 (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 1.99 (s, 3H, $COCH_3$), 2.00 (s, 3H, $COCH_3$), 2.02 (s, 3H, $COCH_3$), 3.69 (s, 3H, $-OCH_3$), 4.20 (d, 1H, $J = 10.1$ Hz, H-5), 5.09 (t, 1H, $J = 9.7$ Hz, H-4), 5.14 (t, 1H, $J = 9.7$ Hz, H-2), 5.43 (t, 1H, $J = 9.5$ Hz, H-3), 5.60 (t, 1H, $J = 9.6$ Hz, H-1), 7.26 (d, 1H, $J = 10.4$ Hz, N–H), 7.43 (m, 1H, Ar–H), 7.52 (m, 1H, Ar–H), 7.63 (m, 1H, Ar–H); ^{13}C NMR ($CDCl_3$): δ 21.7, 21.8, 22.0, 54.2, 70.8, 71.1, 72.9, 74.9, 78.8, 113.3, 129.5, 133.0, 146.5, 159.1, 168.1, 170.5, 170.6, 171.7; LRMS calcd for $C_{18}H_{21}NO_{11}$: 427.1, found: 428.1 ($+H^+$).

4.20. *N*-(Methyl 2,3,4-tetra-*O*-acetyl-β-D-glucuronosyl)-2,3,4,5,6-pentafluorobenzamide (26)

Colorless solid (0.395 g, 75%) isolated from flash column chromatography using 2:1 hexane/EtOAc: mp 175–178 °C; $[\alpha]_D$ +42.6 (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 2.02 (s, 3H, $COCH_3$), 2.03 (s, 3H, $COCH_3$), 2.05 (s, 3H, $COCH_3$), 3.71 (s, 3H, $-OCH_3$), 4.21 (d, 1H, $J = 10.1$ Hz, H-5), 5.09 (t, 1H, $J = 9.5$ Hz, H-4), 5.13 (t, 1H, $J = 9.8$ Hz, H-2), 5.41 (t, 1H, $J = 9.5$ Hz, H-3), 5.46 (t, 1H, $J = 9.3$ Hz, H-1), 7.26 (d, 1H, $J = 9.2$ Hz, N–H); ^{13}C NMR ($CDCl_3$): δ 21.7, 21.8, 21.9, 54.1, 70.6, 71.8, 73.3, 74.1, 78.3, 113.0, 138.4 (d, $2\times C$, $J = 251$ Hz), 143.1 (d, $J = 251$ Hz), 144.5 (d, $2\times C$, $J = 251$ Hz), 158.6, 168.6, 170.2, 170.7, 170.8; ESIMS calcd for $C_{20}H_{18}F_5NO_{10}$: 550.0749 (+Na), found: 550.0737 (+Na).

4.21. *N*-(Methyl 2,3,4-tetra-*O*-acetyl-β-D-glucuronosyl)-butyramide (27)

Colorless solid (0.282 g, 70%) isolated from flash column chromatography using 1:1 hexane/EtOAc: mp 81–83 °C; $[\alpha]_D$ +24.1 (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 0.84 (t, 3H, $J = 7.3$ Hz, H_γ), 1.56 (sextet, 2H, $J = 3.7$ Hz, H_β), 1.97 (s, 3H, $COCH_3$), 1.98 (s, 6H, $2\times COCH_3$), 2.10 (t, 2H, $J = 8.0$ Hz, H_α), 3.66 (s, 3H, $-OCH_3$), 4.14 (d, 1H, $J = 10.1$ Hz, H-5), 4.92 (t, 1H, $J = 9.6$ Hz, H-4), 5.08 (t, 1H, $J = 9.8$ Hz, H-2), 5.29 (t, 1H, $J = 8.5$ Hz, H-3), 5.34 (t, 1H, $J = 9.5$ Hz, H-1), 6.59 (d, 1H, $J = 9.5$ Hz, N–H); ^{13}C NMR ($CDCl_3$): δ 14.8, 19.8, 21.7, 21.8, 21.9, 54.1, 70.6, 71.4, 73.0, 74.8, 77.9, 168.1, 170.4, 170.6, 171.6, 174.4; ESIMS calcd for $C_{17}H_{25}NO_{10}$: 426.1376 (+Na), found: 426.1365 (+Na).

4.22. *N*-(Methyl 2,3,4-tetra-*O*-acetyl-β-D-glucuronosyl)-3-methylbutanamide (28)

Colorless solid (0.234 g, 56%) isolated from flash column chromatography using 1:1 hexane/EtOAc: mp

67–70 °C; $[\alpha]_D$ +6.0 (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 0.90 (d, 6H, $J = 11.2$ Hz, H_γ), 0.97 (d, 2H, $J = 6.6$ Hz, H_α), 2.02 (s, 9H, $3 \times COCH_3$), 2.08 (m, 1H, H_β), 3.71 (s, 3H, $-OCH_3$), 4.15 (d, 1H, $J = 9.8$ Hz, H-5), 4.94 (t, 1H, $J = 9.6$ Hz, H-4), 5.12 (t, 1H, $J = 10.1$ Hz, H-2), 5.31 (t, 1H, $J = 9.5$ Hz, H-3), 5.37 (t, 1H, $J = 9.5$ Hz, H-1), 6.39 (d, 1H, $J = 9.3$ Hz, N–H); ^{13}C NMR ($CDCl_3$): δ 21.7, 21.8 ($2 \times C$), 23.4 ($2 \times C$), 27.1, 47.0, 54.1, 70.8, 71.3, 73.1, 74.9, 78.8, 168.1, 170.4, 170.6, 171.7, 173.9; ESIMS calcd for $C_{18}H_{27}NO_{10}$: 440.1533 (+Na), found: 440.1545 (+Na).

4.23. *N*-(Chloro(furan-2-yl)methylene)(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)amine (30)

DPPE (0.518 g, 1.3 mmol) in dry THF (0.1 g/mL) was added dropwise to a solution of azide **5** (0.747 g, 2.0 mmol) and 2-furoyl chloride (0.396 mL, 4.0 mmol) at rt. After stirring for 1 h the solvent was removed under reduced pressure and the residue dissolved in $CHCl_3$ (70 mL) and washed with a satd aq $NaHCO_3$ solution (20 mL), water (20 mL), and the organic layer dried ($MgSO_4$), filtered and concentrated to leave a pale yellow syrup that was subjected to flash column chromatography using 1:1 hexane/EtOAc. The imidoyl chloride was isolated as a colorless solid (0.626 g, 68%): mp 120–122 °C; $[\alpha]_D$ −36.4 (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 1.97 (s, 3H, $COCH_3$), 2.03 (s, 3H, $COCH_3$), 2.06 (s, 3H, $COCH_3$), 2.09 (s, 3H, $COCH_3$), 3.91 (ddd, 1H, $J = 2.4$, 4.8, 10.0 Hz, H-5), 4.19 (dd, 1H, $J = 2.3$, 12.4 Hz, H-6), 4.28 (dd, 1H, $J = 4.9$, 12.4 Hz, H-6′), 5.18–5.38 (m, 4H, H-1, H-2, H-3, H-4), 6.53 (dd, 1H, $J = 1.7$, 3.6 Hz, Ar–H), 7.18 (d, 1H, $J = 3.6$ Hz, Ar–H), 7.61 (d, 1H, $J = 1.7$ Hz, Ar–H); ^{13}C NMR ($CDCl_3$): δ 20.6, 20.7 ($2 \times C$), 20.8, 62.0, 68.2, 71.8, 73.1, 73.6, 89.1, 112.2, 118.8, 136.5, 147.0, 147.2, 168.8, 169.1, 170.0, 170.4; ESIMS calcd For $C_{19}H_{22}ClNO_{10}$: 482.0830 (+Na), found: 482.0835 (+Na).

4.24. 5-(Furan-2-yl)-1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-tetrazole (34)

Sodium azide (0.30 g, 4.61 mmol) and imidoyl chloride **30** (0.53 g, 1.15 mmol) were stirred at rt in dry DMF (3 mL) for 5 h. The solvent was removed under reduced pressure and the residue was partitioned between water (10 mL) and CH_2Cl_2 (10 mL). The aqueous layer was further extracted with CH_2Cl_2 (3×10 mL) and the combined extracts were washed with water (10 mL), dried over $MgSO_4$, and concentrated to a syrup that was then purified by flash column chromatography using 1:2 hexane/EtOAc. Tetrazole **34** was isolated as a colorless syrup (0.51 g, 95%): $[\alpha]_D$ −15.1 (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 1.86 (s, 3H, $COCH_3$), 2.04 (s, 3H, $COCH_3$), 2.06 (s, 3H, $COCH_3$), 2.08 (s, 3H, $COCH_3$), 4.08 (ddd, 1H, $J = 2.5$, 5.1, 10.1, H-5), 4.17 (dd, 1H, $J = 2.4$, 12.6 Hz, H-6), 4.26 (dd, 1H, $J = 5.1$, 12.6 Hz, H-6′), 5.31 (t, 1H, $J = 9.8$ Hz, H-3), 5.45 (t, 1H, $J = 9.4$ Hz, H-4), 6.01 (t, 1H, $J = 9.4$ Hz, H-2), 6.22 (d, 1H, $J = 9.3$ Hz, H-1), 6.70 (dd, 1H, $J = 1.7$, 3.6 Hz, Ar–H), 7.40 (d, 1H, $J = 3.6$ Hz, Ar–H), 7.75 (d, 1H, $J = 1.7$ Hz, Ar–H); ^{13}C NMR ($CDCl_3$): δ 20.3, 20.6 ($2 \times C$), 20.7, 61.5, 67.5, 69.4, 73.1, 74.9, 83.6, 112.5, 116.1, 138.8, 145.9, 146.9, 168.1, 168.9, 170.0, 170.1; ESIMS calcd for $C_{19}H_{22}N_4O_{10}$: 489.1234 (+Na), found: 489.1245 (+Na).

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Supplementary data

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