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Traceless Staudinger Ligation of Glycosyl Azides with Triaryl Phosphines: Stereoselective Synthesis of Glycosyl Amides†

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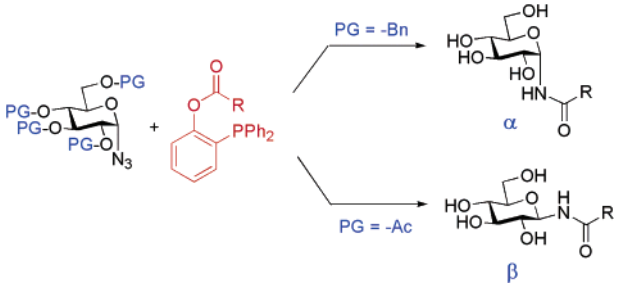

α-Glycosyl amides can be synthesized from the corresponding *O*-benzyl-α-glycosyl azides using a traceless Staudinger ligation with diphenylphosphanyl-phenyl esters **4**. All the phosphines employed and their phenol precursors are stable to air at 4 °C for months. Fast intramolecular trapping of the reduction intermediates results in the direct formation of the amide link, which, in turn, prevents epimerisation and allows retention of configuration at the anomeric carbon. Yields and α-selectivity are high when the reaction is performed in polar aprotic solvents. Removal of the benzyl ether protecting groups is achieved by catalytic hydrogenation. α-Glycosyl amides represent a class of virtually unexplored nonhydrolyzable monosaccharide derivatives that may find a useful application as sugar mimics. Conformational studies by NMR spectroscopy confirm that deprotected α-glycosyl amides in the gluco, galacto, and fuco series retain the normal pyranose conformation of the monosaccharide. The reaction of phosphines **4** with tetra-*O*-acetyl-glycosyl azides is nonstereoconservative, and *β*-glycosyl amides are obtained in good yields and with complete stereoselectivity starting from both α and *β* azides.

Introduction

Glycoproteins and glycolipids play central roles in human health and disease, and their mimetics are interesting candidates for drug development. The chemical synthesis of oligosaccharides and glycoconjugates provides homogeneous material not attainable from biosynthetic systems. Furthemore, chemical synthesis can afford so-called neo-glycoconjugates, unnatural molecules with largely unexplored physicochemical properties, which are finding interesting applications in many fields of glycochemistry and glycobiology.[1] Neo-glycoconjugates are not only useful for the basic understanding of protein−carbohydrate interactions, but they have many practical applications. They are powerful reagents in cell biology studies and excellent tools for the isolation and characterization of animal and plant lectins, for the separation of cells, as well as for the targeting of drugs, artificial vaccines, and diagnostic reagents. Additionally, the synthesis of neo-glycoconjugates is of great interest as a means of obtaining unnatural compounds endowed with new properties. Among these unnatural glycoconjugates, α-linked glycosyl amides appear to be particularly interesting. Natural glycopeptides are almost invariably *β*-linked,[2] hence, it is likely that the unnatural, α-linked isomers may be stable to hydrolytic enzymes and can be used for in vivo applications. Furthermore, it has been recently shown that the peptide conformation of glycopeptides depends on the anomeric configuration of the appended glycan,[3] suggesting that α-linked glycopeptides may give new molecules and materials which behave in an unprecedented fashion.

† Dedicated to Professor Carlo Scolastico on the occasion of his 70th birthday.

(1) Neo-glycoconjugates, part B: biomedical applications. *Methods in Enzymology*; Lee, Y., Lee, R., Abelson, J., Simon, M., Eds.; Academic Press: New York, 1995; Vol. 247.

(2) One example of α-linked glycopeptide has been described: Shibata, S.; Takeda, T.; Natori, Y. *J. Biol. Chem.* **1988**, *263*, 12843−12845.

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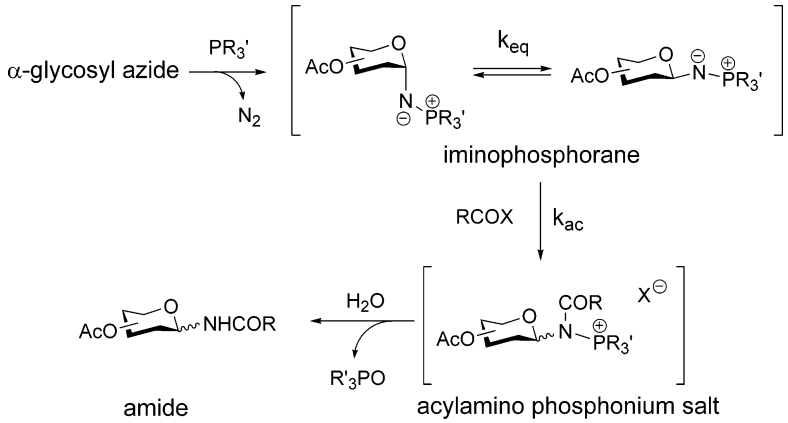
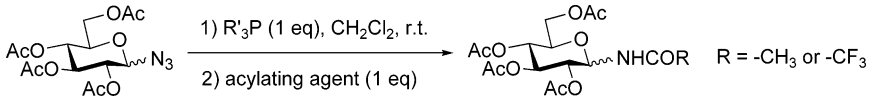
SCHEME 1. Anomeric Isomerization of *O*-Acetyl-glycosyl Iminophosphoranes



SCHEME 2. Staudinger Reduction−Acylation of α-Glycosyl Azides Is Stereoconservative Only with Strong Acylating Agents[15]



	Acylating agent	Yield	2α/2β ratio
1α	$(CH_3CO)_2O$	72	0:100
1α	$(CF_3CO)_2O$	87	78:22
1β	$(CH_3CO)_2O$	72	0:100
1β	$(CF_3CO)_2O$	76	0:100

The most widely employed method for the synthesis of glycosyl amides is the condensation of protected or unprotected glycosylamines[4,5] with carboxylic acid derivatives. Several examples of the reduction of glycosyl azides by catalytic hydrogenation followed by acylation of the resulting glycosylamines have been reported.[6−8] Because glycosylamines rapidly equilibrate to the most stable β-anomer, all the approaches that make use of isolated amine intermediates afford β-glycosyl amides. An alternative methodology attempts to avoid anomeric equilibration by reducing glycosyl azides in the presence of acylating agents.[9−13] The group of Györgydeák investigated in detail the stereochemical course of the reduction−acylation of glycosyl azides by the Staudinger reaction[14] to establish whether α- and β-glycosyl amides can be derived in a stereoselective fashion from the corresponding azides.[15] Working with *O*-acetyl-glycosyl azides, they showed that the Staudinger reduction of glycosyl azides affords aza-ylide intermediates (also called iminophosphoranes; Scheme 1), which can be trapped by acylating agents to give configurationally stable acylamino phosphonium salts that, in turn, yield the corresponding amides upon quenching. However, like glycosylamines, the Staudinger's aza-ylides are also subject to anomeric isomerization, which is biased toward the β-anomers. Thus, the synthesis of β-glycosyl amides can be easily achieved in this process, but in most cases, anomerization remains a significant problem during the synthesis of α-glycosyl amides. In fact, the α/β ratio of the two anomeric amides critically depends on the k_{ac}/k_{eq} ratio (Scheme 1), and good levels of stereoselectivity can be reached only if the acylation step is very fast.

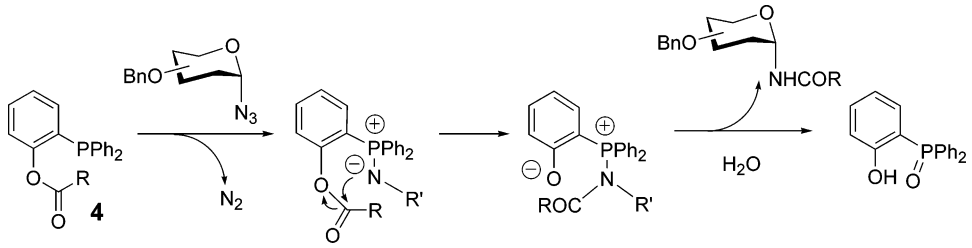
For instance, the reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl azide **1**α with trimethylphosphine followed by acylation with acetic anhydride yields only the β product, while acylation with trifluoroacetic anhydride gives a 78:22 mixture of the α and β anomers, respectively (Scheme 2). Similar results were obtained with 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl azide.[15]

Only a handful of methods have been reported to afford α-glycosyl amides, most of which require two steps and have been described for a limited number of substrates.[16−18]

We have recently reported[19] a general procedure for the reductive acylation of *O*-benzyl-α-glycosyl azides with the functionalized triaryl phosphines **4** (Scheme 3) that are equipped

(3) Bosques, C. J.; Tschampel, S. M.; Woods, R.; Imperiali, B. *J. Am. Chem. Soc.* **2004**, *126*, 8421−8425.
(4) Hackenberger, C. P. R.; O'Reilly, M. K.; Imperiali, B. *J. Org. Chem.* **2005**, *70*, 3574−3578.
(5) Sridhar, P. R.; Prabhu, K. R.; Chandrasekaran, S. *J. Org. Chem.* **2003**, *68*, 5261−5264.
(6) Matsuo, I.; Nakahara, Y.; Ito, Y.; Nukada, T.; Nakahara, T.; Ogawa, T. *Bioorg. Med. Chem.* **1995**, *3*, 1455−1463.
(7) Saha, U. K.; Roy, R. *Tetrahedron Lett.* **1995**, *36*, 3635−3638.
(8) Sabesan, S. *Tetrahedron Lett.* **1997**, *38*, 3127−3130.
(9) Inazu, T.; Kobayashi, K. *Synlett* **1993**, 869−870.
(10) Bosch, I.; Romea, P.; Urpi, F.; Vilarrasa, J. *Tetrahedron Lett.* **1993**, *34*, 4671−4674.
(11) Boullanger, P.; Maunier, V.; Lafont, D. *Carbohydr. Res.* **2000**, *324*, 97−106.
(12) Malkinson, J. P.; Falconer, R. A.; Toth, I. *J. Org. Chem.* **2000**, *65*, 5249−5252.
(13) Shangguan, N.; Katukojvala, S.; Greenberg, R.; Williams, L. J. *J. Am. Chem. Soc.* **2003**, *125*, 7754−7755.
(14) (a) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635−646. (b) Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353−1407.
(15) Kovács, L.; Ösz, E.; Domokos, V.; Holzer, W.; Györgydeák, Z. *Tetrahedron* **2001**, *57*, 4609−4621.
(16) Ratcliffe, A. J.; Fraser-Reid, B. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1805−1810. Ratcliffe, A. J.; Konradsson, P.; Fraser-Reid, B. *J. Carbohydr. Res.* **1991**, *216*, 323−335.
(17) Damkaci, F.; DeShong, P. *J. Am. Chem. Soc.* **2003**, *125*, 4408−4409.
(18) Bianchi A. PhD Thesis, Universita' di Milano, 2004−2005.
(19) (a) Bianchi, A.; Bernardi, A. *Tetrahedron Lett.* **2004**, *45*, 2231−2234. (b) Bianchi, A.; Russo, A.; Bernardi, A. *Tetrahedron: Asymmetry* **2005**, *16*, 381−386.

SCHEME 3. Traceless Staudinger Ligation of α-Glycosyl Azides with Phosphines 4[19]

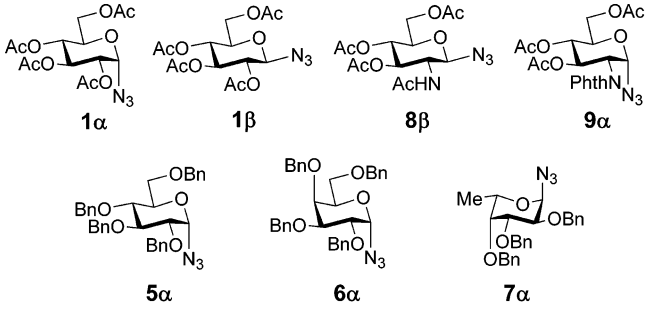


to effect intramolecular acyl transfer after the azide reduction step has generated the intermediate iminophosphorane.

This traceless Staudinger ligation[20,21] proceeds with retention of configuration at the anomeric carbon and was applied to *O*-benzyl glycosyl azides in the fuco, gluco, and galacto series to afford the corresponding α-glycosyl amides with good yields and stereoselectivities for a range of acyl chains. This first group of experiments provided the first general method for the synthesis of α-glycosyl amides, however, various problems were left unsolved. In particular, steric hindrance of the acyl chain to be ligated appeared to slow the acyl transfer step, and often phosphotriazadiene intermediates were isolated rather than the expected amides.[19b] In some cases, low reactivity could be overcome by sunlamp irradiation of the reaction mixture, but the effect did not appear to be general, and the results varied unpredictably with the type of substrate. When irradiation failed, we found that purification of the intermediates from the reaction mixtures allowed them to evolve spontaneously to the amide products, which had to be separated from the phosphine oxide byproduct. Hence, the final compounds could be obtained only after two chromatographic isolations.[19b]

During the course of these studies, Kiessling and co-workers published a paper on the traceless ligation of *O*-acetyl-glycosyl azides with dialkylphosphino(borane)methanethioesters to give *β*-glycosyl amides.[22] Their work showed that the reaction is sensitive to the polarity of the solvent and, in particular, it occurs with higher yields in dipolar aprotic media. Similar observations were reported in a mechanistic study from the Bertozzi laboratory, showing that the Staudinger ligation proceeds faster in solvents with higher dielectric constants.[23] Our initial results on glycosyl azides had been obtained in solvents of relatively low polarity, typically toluene or chloroform.[19] The new literature reports prompted a re-examination of the solvent effect in the ligation of *O*-benzyl-glycosyl azides with phosphines **4**, and the results are reported in this paper. We found that the ligation is indeed accelerated using polar aprotic solvents, such as *N*,*N*-dimethylformamide (DMF) or *N*,*N*-dimethylacetamide (DMA). Under these improved conditions, the reaction of tetra-*O*-benzyl-α-glucosyl and α-galactosyl azides was found to be stereoconservative and to afford the corresponding α-glycosyl amides in good yields and with good stereoselectivity for a broad range of linear and branched acylating agents. We also studied the reactivity of phosphines **4** as Staudinger ligation agents for

CHART 1. Glycosyl Azides Used in This Study



O-acetyl-glycosyl azides. With these substrates, the reaction was found to be *β*-selective starting from both α- and *β*-tetra-*O*-acetyl azides. This study establishes the diphenylphosphanyl-phenyl esters **4** as powerful agents for the stereoselective Staudinger ligation of glycosyl azides to give glycosyl amides either in the α or *β* configuration, depending on the configuration of the starting azide and on the oxygen protecting groups in the starting monosaccharide. Phosphines **4** are air stable reagents that can be easily synthesized and purified by flash chromatography, which gives a significant advantage over other ligation reagents,[22] and their application in the stereoselective synthesis of glycosyl amides should be particularly useful.

Results and Discussion

Synthesis of the Starting Materials and Reagents. The azides **1** and **5**−**9** (Chart 1) used in this study are all known compounds. Their synthesis and characterization are reported in the Supporting Information. The 2,3,4,6-tetra-*O*-acetyl-*β*-D-glucosyl azide **1*β***[24] was synthesized with complete stereocontrol by treating glucose pentaacetate with trimethylsilyl azide and tin tetrachloride, as described by Paulsen.[25] The 2,3,4,6-tetra-*O*-acetyl-α-D-glucosyl azide **1α**,[24] the 3,4,6-tri-*O*-acetyl-2-*N*-acetyl-2-deoxy-*β*-D-glucopyranosyl azide **8*β***,[26] and the 3,4,6-tri-*O*-acetyl-2-*N*-phthalimido-2-deoxy-α-D-glucopyranosyl azide **9α**[26] were stereoselectively prepared by S_N2 displacement of the corresponding anomeric halides[27] with sodium azide [28] or

(20) (a) Saxon, E.; Bertozzi, C. R. *Science* **2000**, *287*, 2007−2010. (b) Saxon, E.; Armstrong, J. I.; Bertozzi, C. R. *Org. Lett.* **2000**, *2*, 2141−2143. (c) Nillson, B. L.; Kiessling, L. L.; Raines, R. T. *Org. Lett.* **2000**, *2*, 1939−1941.

(21) Koehn, M.; Breinbauer, R. *Angew. Chem., Int. Ed.* **2004**, *43*, 3106−3116 and referencs therein.

(22) He, Y.; Hinklin, R. J.; Chang, J.; Kiessling, L. L. *Org. Lett.* **2004**, *6*, 4479−4482.

(23) Lin, F. L.; Hoyt, H. M.; van Halbeek, H.; Bergman, R. G.; Bertozzi, C. *J. Am. Chem. Soc.* **2005**, *127*, 2686−2695.

(24) (a) Ogawa, T.; Nakabayashi, S.; Shibata, S. *Agric. Biol. Chem.* **1983**, *47*, 281−285. (b) Sabesan, S.; Neira, S. *Carbohydr. Res.* **1992**, *223*, 169−185.

(25) (a) Paulsen H. *Adv. Carbohydr. Chem.* **1971**, *26*, 127. (b) Györgydeák, Z.; Szilágyi, L.; Paulsen H. *J. Carbohydr. Chem.* **1993**, *12*, 139−163.

(26) Szylágyi, L.; Györgydeák, Z. *Carbohydr. Res*. **1985**, *143*, 21−41.

(27) 2,3,4,6-tetra-*O*-acetyl-*β*-D-glucosyl chloride: Korytnyk, W.; Mills J. A. *J. Chem. Soc.* **1959**, 636−649. 3,4,6-tri-*O*-acetyl-2-*N*-acetyl-2-deoxy-α-D-glucopyranosyl chloride: Martichonok, V.; Whitesides, G. M. *J. Org. Chem.* **1996**, *61*, 1702−1706. 2-*N*-phthalimido-2-deoxy-3,4,6-tri-*O*-acetyl-*β*-D-glucopyranosyl bromide: Baluja, G.; Chase, B. H.; Kenner, G. W.; Todd, A. *J. Chem. Soc.* **1960**, 4678−4681.

(28) Tropper, F. D.; Andersson, F. O.; Braun, S.; Roy, R. *Synthesis* **1992**, 618−620.

CHART 2. Functionalized Phosphines 4a−i Used in This Study

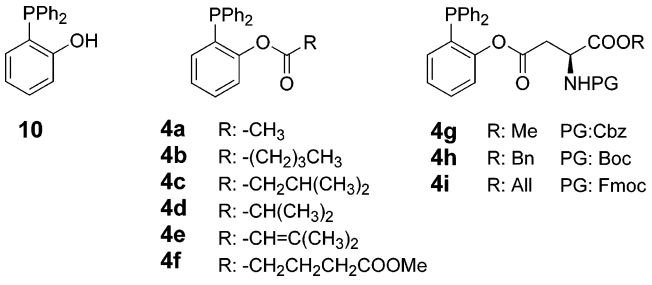


TABLE 1. Staudinger Ligation of the Glycosyl Azide 5α with Phosphines 4a−f

		method A[a] ($CHCl_3$, hν)		method B[b] (DMF)	
phosphine	product	yield[c] (%)	α/β ratio[d]	yield[c] (%)	α/β ratio[d]
4a	**11a**	77[e]	>99:1		
4b	**11b**	70	84:16	83	93:7
4c	**11c**	60	83:17	81	95:5
4d	**11d**	40	84:16	76	>97:3
4e	**11e**	65[e]	85:15	56	>97:3
4f	**11f**			65	93:7

[a] Reaction performed in CCl_4, from ref 19b. [b] Phosphine (1.2 equiv), DMF, 70 °C, 18 h, then H_2O, 70 °C, 2 h. [c] Isolated yield. [d] Determined by ^1H NMR. [e] No irradiation required.

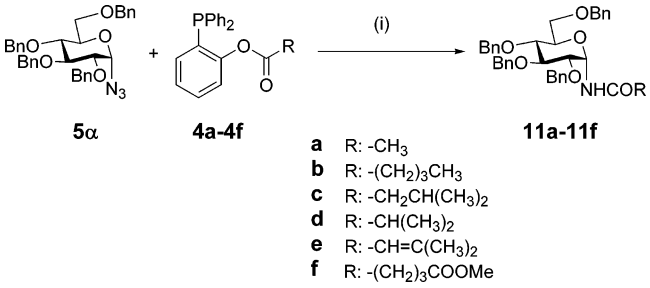
trimethylsilyl azide and tetrabutylammonium fluoride.[29] The 2,3,4,6-tetra-*O*-benzyl-α-D-glucosyl azide **5α**[19a] and the 2,3,4,6-tetra-*O*-benzyl-α-D-galactosyl azide **6α**[19a] were obtained as 70:30 mixtures of the easily separable α and β anomers from the corresponding anomeric acetates with trimethylsilyl azide and tin tetrachloride.[25] The completely stereocontrolled synthesis of 2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl azide **7α** from the β-iodide[30] was previously reported.[19a]

The functionalized phosphines employed are collected in Chart 2. They were synthesized from the known *o*-diphenylphosphinophenol **10**[31] using partially reported procedures.[19b] Their synthesis and characterization are reported in the Supporting Information. All the phosphines studied and their phenol precursors were stable to air at 4 °C for months. They could be purified by flash chromatography and generally handled with no special precautions.

Traceless Staudinger Ligation of the Glycosyl Azides. Ligation of the Perbenzylated Glycosyl Azides. In a first set of experiments, ligation of 2,3,4,6-tetra-*O*-benzyl-α-D-glucosyl azide **5α** with phosphines **4a−i** in DMF was examined and compared with the results previously obtained in $CHCl_3$ (Table 1, method A and Scheme 4).

In DMF (Table 1, method B) the acyl transfer step was indeed faster than in $CHCl_3$, and irradiation of the reaction mixture was not required to achieve complete conversion of the intermediates. Gratifyingly, higher yields and selectivities were also achieved. Under these conditions (DMF at 70 °C for 18 h, then water, at the same temperature for 2 h), the α-stereoselectivity was improved to synthetically useful levels, and in all the cases, the α/β ratios were higher than 93:7.

SCHEME 4. Staudinger Ligation of the 2,3,4,6-Tetra-*O*-benzyl-α-D-glucosyl Azide 5α with Phosphines 4a−f[a]



[a] Reagents and conditions: (i) (a) DMF, 70 °C, 20 h; (b) H_2O, 70 °C, 2 h.

Similar results were obtained starting from tetra-*O*-benzyl-α-D-galactosyl azide **6α**. For instance, product **12c** was obtained in good yield and with high stereoselectivity (70% and 98:2 α/β ratio) using phosphine **4c** (Scheme 5).

N-linked glycopeptides are connected to the peptide aglycon via the side chain of an Asn residue,[32] therefore, *N*-glycosylation of the aspartic acid side chain appears particularly useful to obtain neo-glycopeptides. In our previous studies,[19b] however, acyl transfer from the aspartic acid 4-(2-diphenylphosphanylphenyl)ester **4g** was found to be highly problematic; the reaction with *O*-benzyl-α-D-glucosyl azide **5α** in toluene or in $CHCl_3$ afforded a pair of diastereomeric intermediates that were tentatively assigned the phosphotriazadiene structures shown in Figure 1. Conversion of the intermediates could not be obtained in the reaction mixtures under a variety of conditions, including sunlamp irradiation, but occurred spontaneously after chromatographic isolation to yield an 86:14 α/β mixture of azides **11g**, which had to be further purified from the phosphinoxide byproduct. This was particularly frustrating, and the solvent effects on the yield and the selectivity of this Staudinger ligation were extensively studied by testing different polar aprotic solvents. The results are reported in Table 2 and Scheme 6.

In DMF, the conversion of the intermediates to product improved significantly, but the α-stereoselectivity decreased compared to toluene (Table 2, compare entries 1 and 6). In fact, running the ligation in DMF at 70 °C, the amide **11g** was obtained in 51% yield as a 50:50 α/β mixture, and no intermediates were isolated (Scheme 6, Table 2, entry 1). In DMA (entry 2, Table 2), a better conversion was observed (65% yield after 4 h at 70 °C), but the α/β ratio was not improved (50:50 α/β ratio). Other polar solvents, like acetonitrile and dimethyl sulfoxide (entry 3 and 4, Table 2), did not improved the α-selectivity (35:65 and 50:50 α/β ratio, respectively). In 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU, entry 5, Table 2), TLC analysis of the crude reaction mixture apparently showed a good conversion, but the isolation of the products was difficult because of the high boiling point of this solvent. However, a 65:35 α/β mixture was obtained in 43% yield.

The effect of the reaction temperature was also studied (Table 2, entries 7 and 8). In DMA at 110 °C, the yield of the reaction was poor (42%) but, most importantly, the selectivity was shifted in favor of the β epimer (24:76 α/β) (entry 7, Table 2). Surprisingly, similar results were also obtained running the

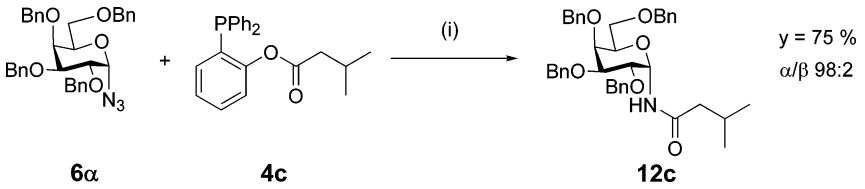
(29) Soli, E. D.; Manoso, A. S.; Patterson, M. C.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 3171−3177.

(30) (a) Gervay, J.; Nguyen, T. N.; Hadd, M. J. *Carbohydr. Res.* **1997**, *300*, 119−125. (b) Hadd, M. J.; Gervay, J. *Carbohydr. Res.* **1999**, *320*, 61−69.

(31) Rauchfuss, T. B. *Inorg. Chem.* **1977**, *16*, 2966−2968.

(32) Herzner, H.; Reipen, T.; Schultz, M.; Kunz, H. *Chem. Rev.* **2000**, *100*, 4495−4537.

SCHEME 5. Staudinger Ligation of the Azide 2,3,4,6-Tetra-*O*-benzyl-α-D-galactosyl Azide 6α with Phosphine 4c[a]



[a] Reagents and conditions: (i) (a) DMF, 70 °C, 20 h; (b) H_2O, 70 °C, 2 h.

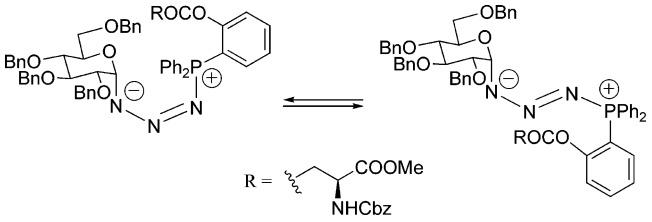


FIGURE 1. Tentative structure of the stereoisomeric intermediates isolated from the reaction of **5α** and **4g** in toluene (from ref 19b).

TABLE 2. Staudinger Ligation of Azide 5α with Phosphine 4g[a]

entry	reaction conditions	yield[b] (%)	**11g** α/β ratio[c]
1	DMF, 70 °C, 18 h	51	50:50
2	DMA, 70 °C, 4 h	65	50:50
3	CH_3CN, 70 °C, 4 h	n.d.	35:65
4	DMSO, 70 °C, 4 h	n.d.	50:50
5	DMPU, 70 °C, 18 h	43	65:35
6	toluene, 70 °C, 18 h[d]	75[e]	86:14
7	DMA, 110 °C, 4 h	40	22:78
8	DMA, rt, 18 h	42	24:76

[a] In all cases, the reaction was performed with 1.2 equiv of **4g** at the temperature and for the time indicated, then water was added and the reaction mixture was stirred at the indicated temperature for 4−18 h. [b] Isolated yields. [c] Determined by ^{1}H NMR. [d] From ref 19b. [e] After two chromatographic isolations.

ligation at room temperature (entry 8, Table 2). Therefore, a change in the reaction temperature did not improve the α-selectivity.

In conclusion, the best α-selectivity for the ligation was obtained using toluene as the solvent (Table 2, entry 6) but only after isolation of the intermediates and their spontaneous conversion to the amide products.[19b] On the other hand, the best conversion was achieved in DMPU (Table 2, entry 5) or in DMA (Table 2, entry 2), but in these solvents, no stereoselectivity was observed.

Conversion and selectivity were finally optimized using solvent mixtures (Table 3). As expected, increasing the amount of toluene in the mixture improved the α-selectivity, while increasing the amount of DMA accelerated the reaction and led to a higher conversion of the intermediates. The optimal conditions for the synthesis of **11g-α** were shown to be DMA/toluene 1:3 at 70 °C (Table 3, entry 3): under these conditions a 75:25 α/*β* ratio and a 68% yield were obtained. The two isomers **11g-α** and **11g-*β*** were separated by flash chromatography.

TABLE 3. Staudinger Ligation of Azide 5α with Phosphine 4g: Effect of Solvent Mixtures[a]

entry	reaction conditions	yield[b] (%)	α/*β* ratio[c]
1	DMA/toluene 3:1, 4 h	n.d.	55:45
2	DMA/toluene 1:1, 4 h	84	61:39
3	DMA/toluene 1:3, 4 h	68	75:25
4	DMA/toluene 1:9, 24 h	59	75:25
5	DMPU/toluene 1:1, 24 h	56	54:46
6	DMPU/toluene 1:9, 24 h	63	79:21

[a] In all cases, the reaction was performed with 1.2 equiv of **4g** at 70 °C for the time indicated, then water was added and the reaction mixture was stirred at room temperature for18 h. [b] Isolated yields. [c] Determined by ^{1}H NMR.

Mixtures of DMPU and toluene were also used (Table 3, entries 5 and 6). The best mixture was in this case 1:9 DMPU/toluene, leading to a 79:21 α/*β* ratio (entry 6, Table 3). However, even if the α-selectivity is slightly higher, the use of DMA/toluene 1:3 is preferable from a practical standpoint, because the high boiling point of DMPU complicates the isolation of the products at the end of the reaction.

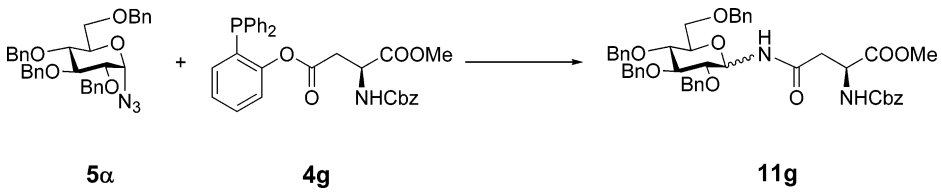
The nature of the protecting groups on the amino acid does not appear to affect either the stereoselectivity or the yield of the reaction to a significant extent (Scheme 7). So ligation of **5α** with phosphine **4h** (NHBoc, benzyl ester) or **4i** (NHFmoc, allyl ester) gave a mixture of the two isomers in about a 3:1 α/*β* ratio (Scheme 7), and also, in these cases, the anomers can be separated by flash chromatography.

Similar results were obtained starting from 2,3,4,6-tetra-*O*-benzyl-α-D-galactosyl azide **6α**, using the conditions optimized for the synthesis of **11g**−**i** (Scheme 8). However, the α-selectivity is lower and the chromatographic separation of the anomers appears more difficult.

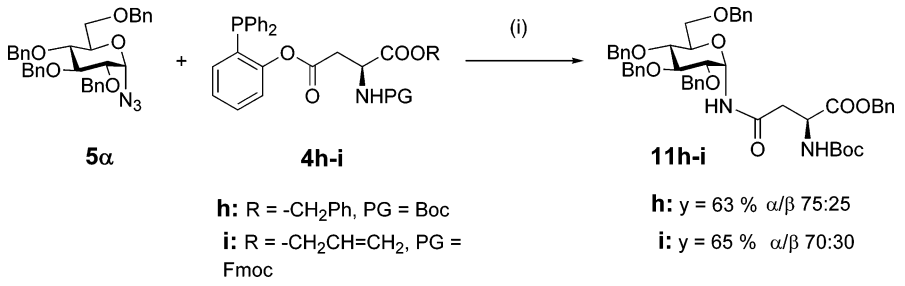
Ligation of the Peracetylated Glycosyl Azides. Phosphines **4** appeared to perform remarkably well in the Staudinger ligation of *O*-benzyl-glycosyl azides. They also are very stable reagents and easy to synthesize. We, therefore, decided to explore their use in the ligation of *O*-acetyl-glycosyl azides. These substrates have often been transformed in *β*-glycosyl amides using Staudinger reduction−acetylation sequences[11,12,15,33] or, more recently, by Staudinger ligation with dialkylphosphino(borane)-methanethioesters.[22] The latter conditions were reported by Kiessling and co-workers to yield *β*-glycosyl amides, irrespective of the configuration of the starting azide.

The first attempts to obtain ligation from peracetylated azides were conducted by reacting the 2,3,4,6-tetra-*O*-acetyl-*β*-D-

SCHEME 6. Staudinger Ligation of Azide 5α with Phosphine 4g

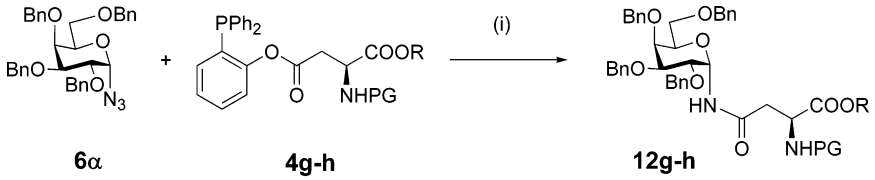


SCHEME 7. Staudinger Ligation of Azide 5α with Phosphines 4h and 4i[a]



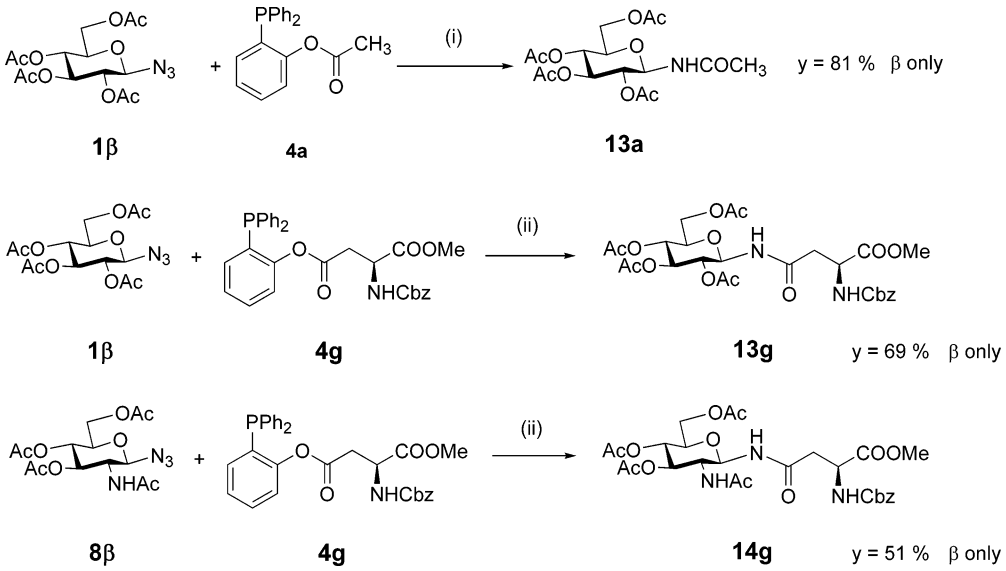
[a] Reagents and conditions: (i) (a) 1:3 DMA/toluene, 70 °C, 4 h; (b) H_2O, 70 °C, 18 h.

SCHEME 8. Staudinger Ligation of Azide 6α with Phosphines 4g and 4h[a]



[a] Reagents and conditions: (i) (a) 1:3 DMA/toluene, 70 °C, 4 h; (b) H_2O, 70 °C, 18 h.

SCHEME 9. Staudinger Ligation *O*-Acetyl-*β*-azides 1*β* and 8*β*[a]



[a] Reagents and conditions: (i) $CHCl_3$, 70 °C, 24 h; (ii) (a) DMA, 70 °C, 4 h; (b) H_2O, 70 °C, 18 h.

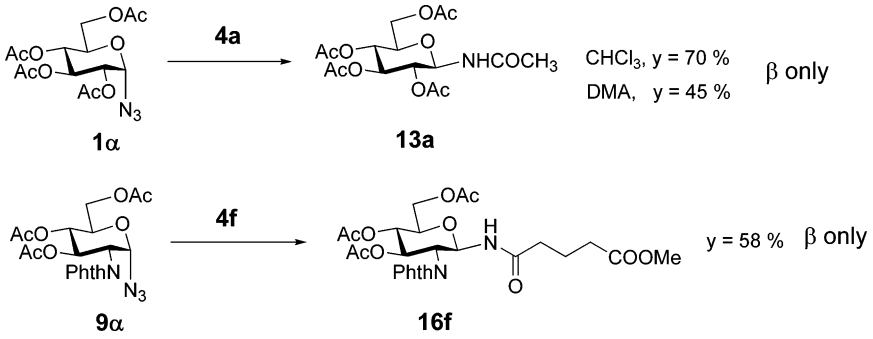
glucopyranosyl azide **1*β*** with diphenylphosphanyl-phenyl acetate **4a** in $CHCl_3$ (Scheme 9). At 70 °C for 24 h clean ligation was observed and the corresponding glucosyl acetamide **13a** was isolated in 81% yield (Scheme 9).

Acyl transfer from phosphine **4g** proved to be more difficult, and reduction intermediates were isolated running the reaction in $CHCl_3$ or toluene. However, clean ligation was obtained in DMA (70 °C, 4 h) to give the glycosyl amino acid **13g** with complete *β*-stereoselectivity and in 69% yield (Scheme 9). The same phosphine was used under the same conditions for the synthesis of the glycosyl amino acid **14j** (Scheme 9), starting from the 3,4,6-tri-*O*-acetyl-2-*N*-acetyl-2-deoxy-*β*-D-glucopyranosyl azide **8*β***. Again, the product was obtained with complete *β*-stereoselectivity and in 51% yield.

To evaluate the behavior of *O*-acetyl α-azides in these Staudinger ligations, the same reactions were performed using the 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl azide **1α**. When the ligation was run with phosphine **4a**, either in $CHCl_3$ or in DMA, only the corresponding *β*-acetamide *β*-**13a** was isolated in 70 and 45% yield, respectively (Scheme 10). Similarly, *β*-selectivity was observed when the Staudinger ligation was performed on the 3,4,6-tri-*O*-acetyl-2-*N*-phthalimido-2-deoxy-α-D-glucopyranosyl azide **9α**. For instance, the *β*-glycosyl amide **16f** was isolated in 58% yield by treating **9α** with phosphine **4f** in DMF at 70 °C for 20 h before adding water (Scheme 10).

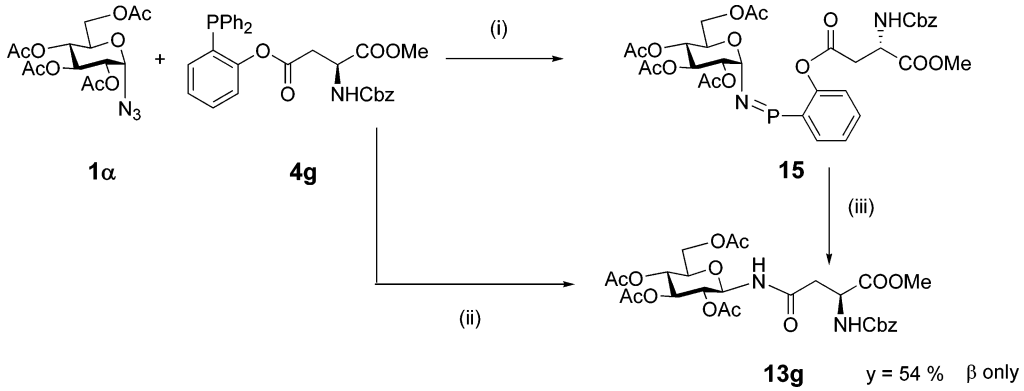
(33) (a) Inazu, T.; Kobayashi, K. *Synlett* **1993**, 869−870. (b) Bosch, I.; Romea, P.; Urpi, F.; Vilarrasa, J. *Tetrahedron Lett.* **1993**, *34*, 4671−4674.

SCHEME 10. Staudinger Ligation of *O*-Acetyl α-azides 1α and 9α[a]



[a] Reagents and conditions: (i) (a) DMF, 70 °C, 22 h; (b) H_2O, 70 °C, 20 h.

SCHEME 11. Staudinger Ligation of Azide 1α with Phosphine 4g[a]



[a] Reagents and conditions: (i) (a) DMA, rt, 2 h; (b) 40 °C, 4 h; (ii) (a) DMA, 70 °C, 2 h; (b) H_2O, 70 °C, 18 h; (iii) H_2O, 70 °C, 18 h.

The reaction with phosphine **4g** was also extensively studied (Scheme 11). In DMA at 70 °C, only the *β*-anomer (compound **13g**) was obtained in 54% yield, thus, with complete inversion of the anomeric configuration of the starting azide **1α**. Lowering the reaction temperature to 40 °C led to the isolation of the α-iminophosphorane intermediate **15** (Scheme 11; ^{1}H NMR, $CDCl_3$, 400 MHz: H_1, 5.29 ppm, dd, $J_{1-2} = 3.7$ Hz, $J_{1-P} = 22.6$ Hz) from which only the *β*-amide **13g** was slowly formed upon addition of water. Peracetylated glycosyl iminophosphoranes are more stable than their perbenzylated analogues and have been previously isolated and observed by ^{1}H NMR spectroscopy.[15,34,35] The same stereochemical outcome was obtained by running the ligation in 1:3 DMA/toluene mixtures: again, the only product isolated at the end of the reaction was the *β*-amide *β*-**13g** (yield 51%).

Thus, the anomeric iminophosphoranes of *O*-acetyl sugars appear to react more sluggishly than the corresponding *O*-benzyl derivatives with acylating agents and to allow α to *β* anomerization to occur prior to acyl transfer. Unlike the ligation of tetra-*O*-benzyl-glycosyl azides, the reduction−acylation of tetra-*O*-acetyl-glycosyl azides is a nonstereoconservative process, and acyl transfer occurs more slowly than iminophosphorane anomerisation. These results are in agreement with recent literature reports obtained by the Kiessling group using dialkylphosphino-(borane)methanethioesters.[22]

α-Glycosyl Amides: Deprotection, Characterization, and Conformational Analysis. Removal of the benzyl ether protecting groups from compounds **17a**, **11a**, **12a**,[19a] **11b**, **11g** and **11h** was achieved by catalytic hydrogenation (Scheme 12). The acetamides **17a**, **11a**, and **12a** were deprotected with Pd−C in MeOH under 1 atm of H_2; the pentanamide **11b** required a slight H_2 pressure (3 atm) and the *N*-aspartyl derivatives **11g** and **11h** were deprotected using 3 bar of H_2 and a 85:10:5 DMA/H_2O/AcOH mixture as solvent[36] (Scheme 12).

The N^{γ}-(α-D-glucopyranosyl)-L-asparagine-*O*-methyl ester **19g** was then acetylated (Ac_2O, pyridine, DMAP catalyst), and the ^{1}H and ^{13}C NMR spectra of **20g** were found to be consistent with those reported for the corresponding benzyl ester[17] (Scheme 12).

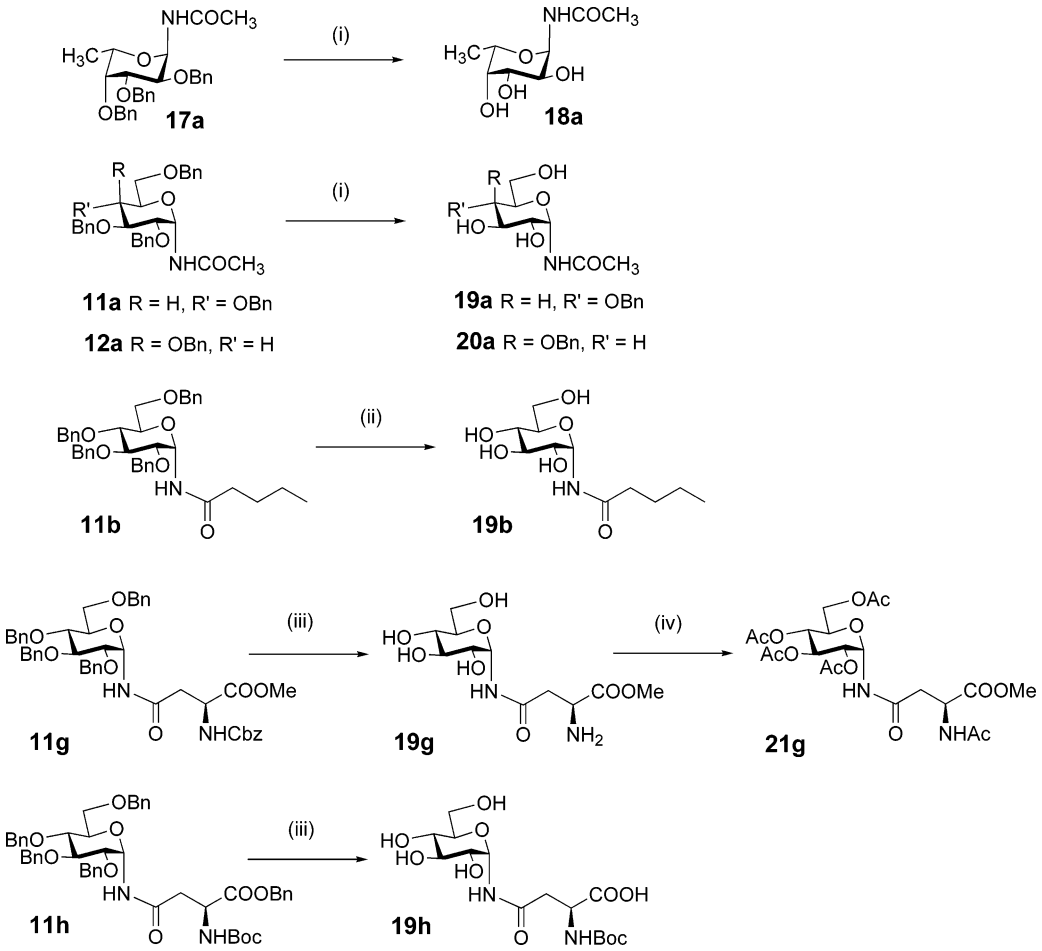
The pyranose conformation of the α-glycosyl acetamides **18a**−**20a** (Figure 2) was determined by NMR spectroscopy (D_2O, 298 K). The NOE contacts observed for each product are schematically represented in Figure 1 (see Supporting Information Table SI-1 for further details). Analysis of the coupling constants and of the NOESY spectra allowed us to establish that the α-glucosyl acetamide **19a** and the α-galactosyl acetamide **20a** adopt the $^4C_1$ conformation, whereas the α-fucosyl amide **18a** adopts a $^1C_4$ conformation. Thus, all the α-glycosyl amides examined so far appear to maintain the normal pyranose conformation of the monosaccharide, which represents an important feature for their use as sugar mimics.

(34) (a) Kovács, L.; Pintér, I.; Messmer, A. *Carbohydr. Res.* **1985**, *141*, 57−65. (b) Kovács, L.; Pintér, I.; Messmer, A. *Carbohydr. Res.* **1987**, *166*, 101−111.

(35) Johnson, A. W. *Ylides and Imines of Phosphorus*; Wiley: New York, 1993.

(36) Tachibana, Y.; Matsubara, N.; Nakajima, F.; Tsuda, T.; Tsuda, S.; Monde, K.; Nishimura, S. I. *Tetrahedron* **2002**, *58*, 10213−10224.

SCHEME 12. Deprotection of *O*-Benzyl-α-glycosyl Amides 17a, 11a, 12a, 11b, 11g, and 11h[a]



[a] Reagents and conditions: (i) H_2, Pd−C, MeOH; (ii) H_2, 3 atm, Pd−C, MeOH; (iii) H_2, 3 atm, Pd−C, 85:15:5 DMA, acetic acid, water; (iv) Ac_2O, DMAP, pyridine.

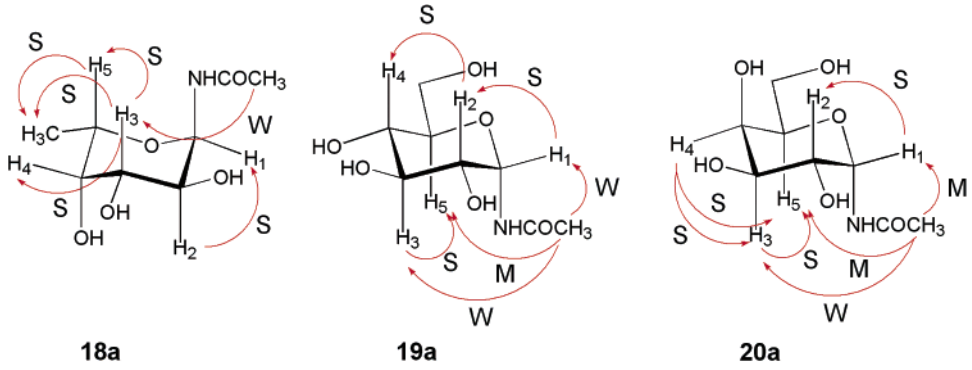


FIGURE 2. NOESY contacts in the α-acetamides **18a**−**20a** (S, strong; M, medium, W, weak).

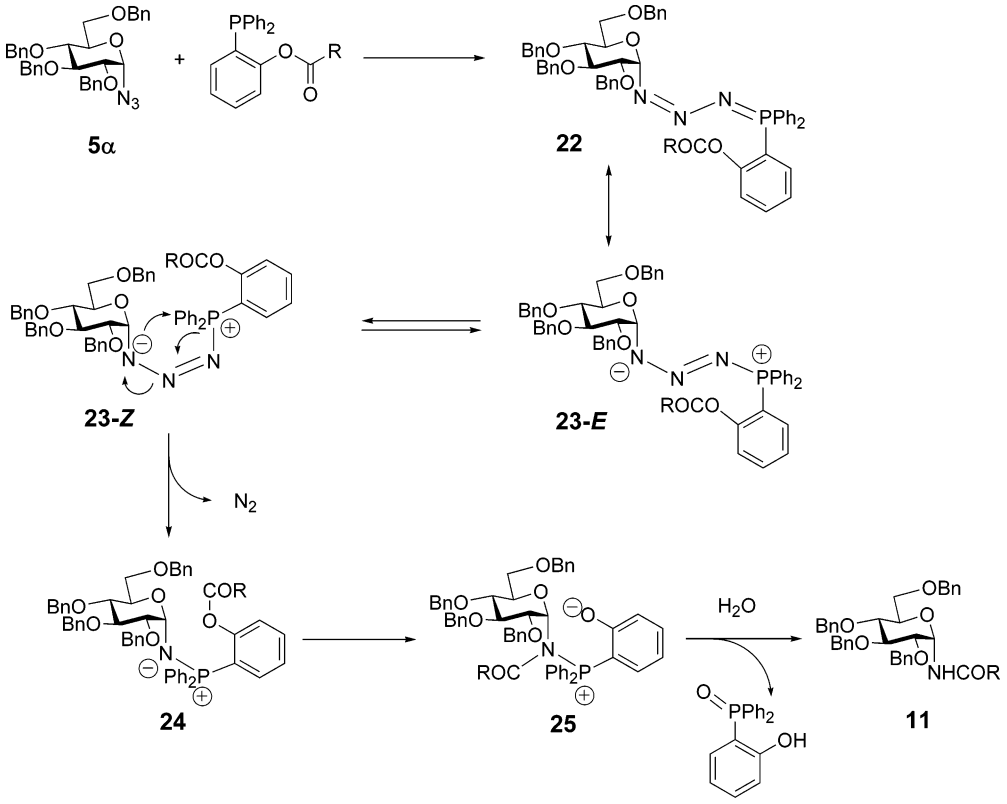
Discussion

The traceless Staudinger ligation represents one interesting approach to the synthesis of glycosyl amides starting from the corresponding azides. In principle the reaction allows for reduction of the starting material and fast intramolecular trapping of the reduction intermediates and should therefore result in the direct formation of the amide link. This in turn should prevent epimerization and allow retention of configuration at the anomeric carbon. Indeed, the studies described here show that these expectations are indeed true if the ligation is performed starting from *O*-benzyl glycosyl azides, whereas anomerization to the *β*-epimer is invariably observed starting from *O*-acetyl-glycosyl azides.

Although the Staudinger reaction has been known from 1919, and actually described before the Wittig counterpart, the mechanism of this reaction is poorly understood. The Staudinger reaction and its mechanism were reviewed by Gololobov et al. in 1981[37] and 1992.[14b] More recently, mechanistic studies were

(37) Gololobov, Y. G.; Zhmurova, I. N.; Kasukhin, L. F. *Tetrahedron* **1981**, *37*, 437−472.

SCHEME 13. Proposed Mechanism for the Staudinger Ligation



reported both using computational methods[38] and using experimental techniques.[23] The number of the intermediates and possible reaction pathways connecting them to each other and to the starting and final products is high, and the potential energy surface is extremely complex. A likely mechanistic scheme for our reactions is shown in Scheme 13 and will be used to discuss the many features that are left unexplained by the studies described above.

The accepted mechanism for the Staudinger reduction of azides with phosphines[14b] requires the formation of two sequential intermediates. The initial nucleophilic attack of the phosphine on the azide is expected to proceed through a phosphotriazadiene **22** (often called phosphotriazene or phosphazene or phosphazide), which should be present as an equilibrating *Z*−*E* mixture of zwitterions (**23-*Z*** and **23-*E***). This intermediate is stabilized by electron-donating groups on the phosphine, electron-withdrawing groups on the azide, or sterically hindering groups on both the phosphine and the azide.[37] Phosphotriazadienes have been isolated from Staudinger azide reductions and characterized by X-ray crystallography and other techniques[14b,15,37,39,40] as zwitterionic species displaying a partial double bond character at the central N−N linkage. The *E* configuration of the N−N double bond (**23-*E***, Scheme 13) is generally observed,[38] while the *Z* configuration has rarely been isolated.[38a] In the reaction mixture, however, **23-*E*** can isomerize to the Z isomer **23-*Z***, which should decompose to afford N_2 and the iminophosphorane **24**. Glycosyl iminophosphoranes are relatively stable species that have been isolated and characterized in many instances.[15,34,35] In the presence of acylating agents, the iminophosphorane reacts at nitrogen to give, after hydrolysis, the corresponding amide. In the traceless ligations under study, intramolecular trapping of the iminophosphorane should occur to afford **24**. It appears that starting from tetra-*O*-benzyl-glycosyl azides this process is faster than the anomeric equilibration of **23**, thus allowing for retention of the anomeric configuration of the starting azide. We speculate that tetra-*O*-acetyl-glycosyl iminophosphoranes may be deactivated toward acyl transfer by the electron-withdrawing effect of the acetates,[41] which delocalizes the negative charge on the nitrogen atom and allows anomeric equilibration to occur before the acyl transfer step.

In the course of our studies on the Staudinger ligation of the tetra-*O*-benzyl-α-glucosyl azide **5**α with phosphines **4** in solvents of low polarity[19] (toluene, CCl_4, $CHCl_3$), we could indeed isolate intermediates that are consistent with the structures **23** with *E*/*Z* ratios that probably depend on the steric

(38) (a) Widauer, C.; Grützmacher, H.; Shevchenko, I.; Gramlich, V. *Eur. J. Inorg. Chem.* **1999**, 1659−1664 and references therein. (b) Alajarín, M.; Conesa, C.; Rzepa, H. S. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1811−1814. (c) Tian, W. Q.; Wang, Y. A. *J. Org. Chem.* **2004**, *69*, 4299−4308. (c) Zhang, S.; Wang, Y. A. *J. Chem. Theory Comput.* **2005**, *1*, 353−362.

(39) (a) Molina, P.; López-Leonardo, C.; Llamas-Botía, J.; Foces-Foces, C.; Fernández-Castaño, C. *Tetrahedron* **1996**, *52*, 9629−9642. (b) Alajarín, M.; Molina, P.; López-Lazaro, A.; Foces-Foces, C. *Angew. Chem., Int. Ed.* **1997**, *36*, 67−70.

(40) (a) Hillhouse, G. L.; Goeden, G. V.; Haymore, B. L. *Inorg. Chem.* **1982**, *21*, 2064. (b) Chernega, A. N.; Antipin, M. Y.; Struchkov, Y. T.; Boldeskul, I. E.; Ponomarchuk, M. P.; Kasukhin, L. F.; Kukhar, V. P. *Zh. Obshch. Khim.* **1984**, *54*, 1979. (c) Chidester, C. G.; Szmuszkovicz, J.; Duchamp, D. J.; Laurian, L. G.; Freeman, J. P. *Acta Crystallogr., Sect. C* **1988**, *44*, 1080. (d) Chernega, A. N.; Antipin, M. Y.; Struchkov, Y. T.; Ponomarchuk, M. P.; Kasukhin, L. F.; Kukhar, V. P. *Zh. Obshch. Khim.* **1989**, *59*, 1256. (e) Tolmachev, A. A.; Kostyuk, A. N.; Kozlov, E. S.; Polishchuk, A. P.; Chernega, A. N. *Zh. Obshch. Khim.* **1992**, *62*, 2675. (f) Goerlich, J. R.; Farkens, M.; Fischer, A.; Jones, P.; Schmutzler, R. *Z. Anorg. Allg. Chem.* **1994**, *620*, 707. (g) Bieger, K.; Bouhadir, G.; Reau, R.; Dahan, F.; Bertrand, G. *J. Am. Chem. Soc.* **1994**, *118*, 8087−8094.

(41) (a) Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583−5584. (b) Ottoson, H.; Udodong, U.; Wu, Z.; Fraser-Reid, B. *J. Org. Chem.* **1990**, *55*, 6068−6070.

hindrance of the acyl group that is transferred (86:14 ratio from **4b** and 50:50 from **4g**). These compounds, once isolated from the reaction mixture by chromatography, appear to evolve rapidly and spontaneously to the amide product. We were unable to fully characterize them or to observe the putative iminophosphorane intermediates. Sunlamp irradiation appeared to accelerate the decomposition of some, but not all, of the intermediates:[19b] the reactions of phosphines **4b**−**d** with **5α** could be driven to completion but the reaction of **4e** and **4g** could not, even using different wavelengths. It is not yet clear if the transfer seen for **4b**−**d** is due to acceleration of the *E* to *Z* isomerization of the N−N double bond in the phosphotriazadiene or to the intervention of a different reaction pathway that facilitates the nitrogen extrusion, nor is it clear why this pathway is not available to phosphotriazadienes formed by **4e** or by the aspartyl phosphine **4g**. Acceleration of the acyl transfer was obtained more reliably using aprotic dipolar solvents. The best results were obtained in DMF or DMA, where the ligation products from *O*-benzyl-α-glycosyl azides were consistently obtained in good yields. An accurate kinetic study of the ligation of glycosyl azides was not performed. The reduction of the azide may well be the rate-determining step of the process when polar aprotic solvents such as DMF are employed. On the contrary, in less polar solvents, the intramolecular acyl transfer is obviously the rate-determining step. The acceleration obtained by sunlamp irradiation may be useful from a preparative point of view, but its scope and the mechanism by which it operates are not yet fully understood. Hence, the use of polar solvents represents a significant advantage for these transformations. In DMA, the ligation appears to have a general scope: various alkyl and alkenyl groups, both linear and branched, were transferred with good results. Functional groups (carbamates, esters, amides) were tolerated both on the azide and on the phosphine. The α/*β* selectivity was also improved in these solvents, but phosphine **4g** represents one exception because the reaction became nonstereoconservative. Starting from *O*-benzyl-α-glycosyl azides, α-glycosyl amides were generally synthesized with high stereoselectivity, although some exceptions were observed. In particular, the transfer of the aspartyl side chain occurred without stereocontrol in DMA and was modestly α-selective using DMA/toluene mixtures. Nonetheless, the method described here represents one of the most general syntheses of α-glycosyl amides. These molecules are almost nonexistent in nature and can potentially be used as nonhydrolyzable mimics of carbohydrates and glycoconjugates. In this respect, it was gratifying to observe that removal of the benzyl protecting groups was straightforward and that the α-glycosyl acetamides that we have synthesized so far appear to retain the ring conformation adopted in the parent pyranose.

The ligation of *O*-acetyl-glycosyl azides with phosphines **4** was found not to be stereoconservative, and *β*-amides were obtained from both α- and *β*-azides. Glycosyl iminophosphoranes were isolated from the ligation of tetra-*O*-acetyl-glucosyl azides **1*β*** and **1α** with phosphines **4**, particularly at low temperature. As discussed above, the reactivity of the Staudinger intermediates is influenced by steric and electronic factors. In our studies, both the acyl phosphine and the starting azide are hindered, which is reported to favor the isolation of phosphotriazadienes and explains the observations on the tetra-*O*-benzyl azide **5α**. The tetra-*O*-acetyl glucosyl azide **1α** may give rise to iminophosphoranes directly because of a diminished steric hindrance relative to the *O*-benzyl azide **5α** or because of electronic effects. Peracetylated compounds are scarcely reactive under the conditions employed, and this difference can be explained considering the arming−disarming effect of the protective groups.[41] The traceless Staudinger ligation of *O*-acetyl glycosyl azides with functionalized phosphines has been described to give *β*-glycosyl amides also using dialkylphosphino(borane)methanethioesters.[22,42] The ligation with phosphines **4** compares favorably with the reported method because it occurs with similar yields and selectivity, but the phosphines are easier to synthesize and handle.

Conclusions

A new method for the stereoselective synthesis of glycosyl amides based on the traceless Staudinger ligation of glycosyl azides with phosphines **4** has been developed and partly optimized. The functionalized phosphine reagents employed in this reaction can be easily prepared on multigram scale. As a result of their stability, they can be handled in air and purified by flash chromatography. The procedure described in this paper has a general scope, and the ligation is tolerant of many alkyl and alkenyl groups, both linear and branched, and of various functional groups.

The reaction of **4** with tetra-*O*-benzyl-α-azides leads to the corresponding α-glycosyl amides in good yields and stereoselectivity when the reaction is performed in polar aprotic solvents such as DMF or DMA . These are the best conditions identified so far for the stereoselective synthesis of α-glycosyl amides via Staudinger ligation. α-Glycosyl amides constitute a class of virtually unexplored nonhydrolyzable monosaccharide derivatives that may find useful applications as sugar mimics. As an initial step, we were able to establish by NMR studies reported in this paper that α-glycosyl amides in the gluco, galacto, and fuco series retain the normal pyranose conformation of the monosaccharide.

On the contrary, the reaction of phosphines **4** with tetra-*O*-acetyl azides is nonstereoconservative, and *β*-glycosyl amides are obtained in good yield and complete stereoselectivity starting from both α- and *β*-azides. The yields and selectivity observed for this reaction in polar solvents compare favorably with the ligation of glycosyl azides recently reported using similar phosphines of lower air stability.[22]

Experimental Section

Azides **1α** and **1*β***,[24] **5α**, **6α**, and **7α**,[19a] **8*β***,[24] and **9α**[26] are all known compounds. Their synthesis is described in the Supporting Information, and some spectroscopic data are shown. The synthesis and the NMR characterization of phosphines **4a**−**4i** are also reported in the Supporting Information. The glycosyl amides **11a**−**11e** have been previously described.[19b]

General Procedure for the Ligation in DMF/DMA. Synthesis of Glycosyl Amides 11b−11f and 12c. The phosphine (**4b**−**4i**, 1.2 mol equiv) was added, at room temperature and under argon, to a solution of the azide **5α** or **6α** (1 mol equiv) in dry (molecular sieves) DMF (0.1 M). The solution was heated to 70 °C and stirred for 4 h. The disappearance of the starting material was monitored by TLC (8:2 toluene/acetone). Then water was added, and the mixture was stirred for 18 h at the same temperature. The solvent was evaporated under reduced pressure, and the crude was purified by flash chromatography.

(42) Grandjean, C.; Boutonnier, A.; Guerreiro, C.; Fournier, J.-M.; Mulard, L. A. *J. Org. Chem.* **2005**, *70*, 7123−7132.

***N*-Pentanedioic Acid 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosylamide Methyl Ester (11f).** Flash chromatography: 55:45 hexane/AcOEt; α/β ratio 97:3; yield = 70%. ^{1}H NMR (400 MHz, $CDCl_3$): 7.47−7.24 (m, 18H, aromatics), 7.17−7.12 (m, 2H, aromatics), 6.29 (d, 1H, NH, J_{1-NH} = 6.7 Hz), 5.81 (dd, 1H, H_1, J_{1-2} = 5.3 Hz, J_{1-NH} = 6.7 Hz), 4.94 (d, 1H, −CH_2Ph, J = 11.0 Hz), 4.82−4.78 (m, 2H, −CH_2Ph), 4.64−4.46 (m, 5H, −CH_2Ph), 4.74 (d, 1H, −CH_2Ph, J = 11.3 Hz), 4.63 (d, 1H, −CH_2Ph, J = 12.1 Hz), 4.55 (d, 1H, −CH_2Ph, J = 10.8 Hz), 3.86−3.60 (m, 6H, H_2, H_3, H_4, H_5, H_6, and $H_{6'}$), 3.76 (s, 3H, $COOCH_3$), 2.38 (m, 2H, −$COCH_2$), 2.31 (t, 2H, −$COCH_2$, J = 7.8 Hz), 1.96 (m, 2H, −$COCH_2$, J = 7.8 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): 173.1, 138.4, 138.1, 137.3, 132.5, 132.0, 128.6, 128.4, 128.1, 128.0, 127.8, 127.8, 81.9, 77.7, 75.4, 75.0, 74.6, 73.6, 72.6, 71.3, 68.4, 51.6, 35.4, 32.9, 29.7, 20.7. ESI-MS: 690.3 (M + Na^+). HRMS (ESI): calculated for $C_{40}H_{45}NO_8$ [M + Na]$^+$, 690.30374; found [M + Na]$^+$, 690.30181.

***N*-(3-Methylbutanoyl)-2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosylamine (12c).** Flash chromatography: 7:3 hexane/AcOEt; α/β ratio 98:2; yield = 70%. ^{1}H NMR (400 MHz, $CDCl_3$): 7.40−7.23 (m, 20H, aromatics), 6.11 (d, 1H, NH, J_{1-NH} = 6.4 Hz), 5.81 (dd, 1H, H_1, J_{1-2} = 4.6 Hz, J_{1-NH} = 6.4 Hz), 4.88−4.40 (m, 8H, −CH_2Ph), 4.10−4.02 (m, 2H, H_2 and H_4), 3.95−3.88 (m, 1H, H_5), 3.73−3.68 (m, 2H, H_6 and $H_{6'}$), 3.65−3.60 (m, 1H, H_3), 2.14−2.02 (m, 3H, −CH_2− and −CH−), 0.98−0.90 (m, 6H, 2 × CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): 173.2, 138.4, 138.3, 137.6, 128.8, 128.5, 128.4, 128.3, 128.0, 127.7, 127.5, 92.0, 77.9, 75.3, 73.8, 73.7, 73.5, 73.0, 72.9, 71.4, 67.8, 46.1, 26.1, 22.5. HRMS (ESI): calculated for $C_{39}H_{45}NO_6$ [M + Na]$^+$, 646.31391; found [M + Na]$^+$, 646.31263.

General Procedure for the Synthesis of Glycosyl Amides 11g−11i and 12g−12h. The phosphine (**4g**−**4i**; 1.2 mol equiv) was added, at room temperature and under argon, to a solution of the azide **5α** or **6α** (1 mol equiv) in a mixture of toluene and DMA 3:1 (0.1 M). The solution was heated to 70 °C and stirred for 4 h. The disappearance of the starting material was monitored by TLC (8:2 toluene/acetone). Then water was added, and the mixture was stirred for 18 h at the same temperature. The solvent was evaporated under reduced pressure, and the crude was purified by flash chromatography.

***N*$^\alpha$-Benzyloxycarbonyl-*N*$^\gamma$-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-L-asparagine-*O*-methyl Ester (11g).** Flash chromatography: 8:2 toluene/AcOEt; α/β ratio 75:25; yield = 68%. ^{1}H 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_{1-2} = 5.1, J_{1-NH} = 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, $COOCH_3$), 2.97 (dd, 1H, −CH_2−CH, J = 5.1, 15.7 Hz), 2.75 (dd, 1H, −CH_2−CH, J = 4.7, 15.7 Hz). ^{13}C NMR (100.6 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. $[\alpha]^{25}_D$ = +37.9 (c = 0.5, $CHCl_3$).

***N*$^\alpha$-*t*-Butoxycarbonyl-*N*$^\gamma$-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-L-asparagine-*O*-benzyl Ester (11h).** Flash chromatography: 7:3 hexane/AcOEt; α/β ratio 75:25; yield = 63%. ^{1}H NMR (400 MHz, $CDCl_3$): 7.36−7.24 (m, 23H, aromatics), 7.13−7.11 (m, 2H, aromatics), 6.40 (d, 1H, N*H*, J = 6.3 Hz), 5.78 (d, 1H, N*H*, J = 8.1 Hz), 5.71 (dd, 1H, H_1, J_{1-2} = 5.3 Hz, J_{1-NH} = 8.1 Hz), 5.18 (d, 1H, COOCH_2Ph, J = 12.2 Hz), 5.14 (d, 1H, COOCH_2-Ph, J = 12.2 Hz), 4.91 (d, 1H, CH_2−Ph, J = 11.0 Hz), 4.80 (d, 1H, CH_2−Ph, J = 11.0 Hz), 4.79 (d, 1H, CH_2−Ph, J = 11.0 Hz), 4.62−4.43 (m, 5H, CH_2−Ph), 3.81 (dd, 1H, H_2, J_{1-2} = 5.3 Hz, J_{2-3} = 9.3 Hz), 3.75−3.57 (m, 5H, H_3, H_4, H_5, H_6, and $H_{6'}$), 2.96 (m, 1H, −CH_2−CH), 2.78 (dd, 1H, −CH_2−CH, J = 4.4, 15.7 Hz), 1.41 (s, 9H, NHBoc). ^{13}C NMR (100.6 MHz, $CDCl_3$): 171.1, 171.0, 138.4, 138.1, 137.9, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.7, 81.9, 77.7, 77.6, 75.5, 75.0, 74.9, 73.6, 72.7, 71.2, 68.3, 67.4, 50.6, 38.2, 28.3. ESI-MS: 867.4 (M + Na^+). HRMS (ESI): calculated for $C_{50}H_{56}N_2O_{10}$ [M + Na]$^+$, 867.38272; found [M + Na]$^+$, 867.38104. IR (Nujol): 3351, 1730, 1715, 1655. $[\alpha]^{25}_D$ = +38.6 (c = 0.5, $CHCl_3$).

***N*$^\alpha$-Fluoren-9-ylmethoxycarbonyl-*N*$^\gamma$-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-L-asparagine-*O*-allyl Ester (11i).** Flash chromatography: 9:1 toluene/AcOEt; α/β ratio 70:30; yield = 65%. ^{1}H NMR (400 MHz, $CDCl_3$): 7.81−7.77 (m, 2H, aromatics Fmoc), 7.65−7.58 (m, 2H, aromatics Fmoc), 7.45−7.12 (m, 24H, aromatics), 6.35 (m, 1H, N*H*−CH), 6.12 (d, 1H, NH−Fmoc, J = 8.0 Hz), 5.91 (m, 1H, =CH), 5.75 (dd, 1H, H_1, J_{1-2} = 4.85 Hz, J_{1-NH} = 8.1 Hz), 5.37−5.30 (m, 1H, =CH_2), 5.27−5.21 (m, 1H, =CH_2), 4.98−4.92 (m, 1H, CH_2−Ph), 4.87−4.80 (m, 2H, −CH_2Ph), 4.76−4.59 (m, 5H, −CH_2Ph), 4.58−4.43 (m, 3H, −C*H*NH, −CH_2All), 4.32−4.21 (m, 2H, Fmoc), 3.85 (dd, 1H, H_2, J_{1-2} = 4.85 Hz, J_{2-3} = 9.1 Hz), 3.83−3.61 (m, 5H, H_3, H_4, H_5, H_6, and $H_{6'}$), 3.11 (dd, 1H, −CH_2−CH, J = 4.9, 17.3 Hz), 2.87 (dd, 1H, −CH_2−CH, J = 4.1, 17.3 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): 170.9, 170.5, 156.3, 143.8, 141.3, 138.4, 137.1, 134.4, 129.1, 128.8, 128.6, 128.4, 128.2, 128.1, 128.0, 127.7, 127.1, 125.2, 125.1, 120.0, 118.7, 81.9, 77.5, 76.9, 75.5, 75.04, 74.97, 73.6, 72.7, 68.3, 67.4, 66.4, 50.8, 47.1, 38.0. ESI-MS: 939.4 (M + Na^+). HRMS (ESI): calculated for $C_{56}H_{56}N_2O_{10}$ [M + Na]$^+$, 939.38272; found [M + Na]$^+$, 939.38034. IR (Nujol): 3353, 1735, 1720, 1651. $[\alpha]^{25}_D$ = +27.5 (c = 0.5, $CHCl_3$).

***N*$^\alpha$-Benzyloxycarbonyl-*N*$^\gamma$-(2,3,4,6-tetra-*O*-benzyl-α/b-D-galactopyranosyl)-L-asparagine-*O*-methyl Ester (12g).** Flash chromatography: 65:35 hexane/AcOEt; α/β ratio 65:35; yield = 65%. ^{1}H NMR (400 MHz, $CDCl_3$; α): 6.31 (d, NH, J_{1-NH} = 6.6 Hz), 5.70 (dd, H_1, J_{1-2} = 4.6 Hz, J_{1-NH} = 6.6 Hz). ^{1}H NMR (400 MHz, $CDCl_3$; β): 5.51 (d, NH, J_{1-NH} = 9.4 Hz), 4.98 (dd, H_1, J_{1-2} = 8.6 Hz, J_{1-NH} = 9.4 Hz).

***N*$^\alpha$-*t*-butoxycarbonyl-*N*$^\gamma$-(2,3,4,6-tetra-*O*-benzyl-α/β-D-galactopyranosyl)-L-asparagine-*O*-benzyl Ester (12h).** Flash chromatography: 70:30 hexane/AcOEt; α/β ratio 68:32; yield = 71%. ^{1}H NMR (400 MHz, $CDCl_3$; α): 6.22 (d, NH, J_{1-NH} = 6.5 Hz), 5.71 (dd, H_1, J_{1-2} = 4.5 Hz, J_{1-NH} = 6.5 Hz). ^{1}H NMR (400 MHz, $CDCl_3$; β): 5.39 (d, NH, J_{1-NH} = 9.0 Hz), 4.99 (dd, H_1, J_{1-2} = 8.4 Hz, J_{1-NH} = 9.0 Hz).

General Procedure for the Deprotection of Glycosyl Acetamides 17a, 11a, and 12a. Synthesis of 18a−20a. A 0.1 M solution of the substrate (1 mol equiv) in MeOH was prepared. The catalyst (10 wt % Pd−C) was added, and the mixture was placed under an atmosphere of hydrogen (1 bar). The mixture was stirred at room temperature for 20 h, and the reaction was monitored by TLC (6:4 toluene/AcOEt and 9:1 $CHCl_3$/MeOH). The catalyst was then filtered on a Celite pad and washed with MeOH. The solvent was removed under reduced pressure.

***N*-Acetyl-α-L-fucopyranosylamine (18a).** Quantitative yield. ^{1}H NMR (400 MHz, D_2O): 5.52 (d, 1H, H_1, J_{1-2} = 5.7 Hz), 3.98 (dd, 1H, H_2, J_{1-2} = 5.7 Hz, J_{2-3} = 10.5 Hz), 3.87 (q, 1H, H_5, J_{4-5} = 0 Hz, J_{5-Me} = 6.5 Hz), 3.80 (dd, 1H, H_3, J_{2-3} = 10.5 Hz, J_{3-4} = 3.4 Hz), 3.76 (d, 1H, H_4, J_{3-4} = 3.4 Hz, J_{4-5} = 0 Hz), 2.04 (s, 3H, −$COCH_3$), 1.14 (d, 3H, −CH_3, J_{5-Me} = 6.5 Hz). ^{13}C NMR (100.6 MHz, D_2O, HETCOR): 76.5, 71.6, 69.5, 67.6, 66.1, 21.9, 15.9.

***N*-Acetyl-α-D-glucopyranosylamine (19a).** Quantitative yield. ^{1}H NMR (500 MHz, D_2O): 5.48 (d, 1H, H_1, J_{1-2} = 5.5 Hz), 3.71 (dd, 1H, H_2, J_{1-2} = 5.5 Hz, J_{2-3} = 10.2 Hz), 3.69−3.66 (m, 2H, H_6 and $H_{6'}$), 3.63 (apparent triplet, 1H, H_3, J_{2-3} = J_{3-4} = 10.2 Hz), 3.43 (m, 1H, H_5), 3.34 (apparent triplet, 1H, H_4, J_{3-4} = J_{4-5} = 10.2 Hz), 2.01 (s, 3H, −CH_3). ^{13}C NMR (125.75 MHz, D_2O, HETCOR): 76.4, 72.9, 72.5, 69.2, 69.2, 60.2, 21.9.

***N*-Acetyl-α-D-galactopyranosylamine (20a).** Quantitative yield. ^{1}H NMR (500 MHz, D_2O): 5.52 (d, 1H, H_1, J_{1-2} = 5.5 Hz), 3.97 (dd, 1H, H_2, J_{1-2} = 5.5 Hz, J_{2-3} = 10.5 Hz), 3.90 (d, 1H, H_4, J_{3-4} = 3.4 Hz, J_{4-5} = 0 Hz), 3.76 (dd, 1H, H_3, J_{2-3} = 10.5 Hz, J_{3-4} =

3.4 Hz), 3.69 (m, 1H, H_5), 3.64−3.61 (m, 2H, H_6 and $H_{6'}$), 2.01 (s, 3H, $-CH_3$). ^{13}C NMR (125.75 MHz, D_2O, HETCOR): 76.6, 71.1, 69.3, 68.8, 66.2, 61.0, 21.9.

Synthesis of *N*-Pentanoyl-α-D-glucopyranosylamine (19b). A solution of the substrate **11b** (10 mg, 0.016 mmol) in MeOH (160 μL, 0.1 M) was prepared. The catalyst (10 wt % Pd−C) was added, and the mixture was placed under an atmosphere of hydrogen (3 bar). The mixture was stirred at room temperature for 6 h, and the reaction was monitored by TLC (6:4 AcOEt/toluene and 8:2 $CHCl_3$/MeOH). The catalyst was then filtered on a Celite pad and washed with MeOH. The solvent was then removed under reduced pressure. Quantitative yield. ^1H NMR (400 MHz, D_2O): 5.60 (d, 1H, H_1, $J_{1-2} = 5.4$ Hz), 3.83 (dd, 1H, H_2, $J_{1-2} = 5.4$ Hz, $J_{2-3} = 9.4$ Hz), 3.86−3.71 (m, 3H, H_3, H_6, and $H_{6'}$), 3.53−3.49 (m, 1H, H_5), 3.46 (apparent triplet, 1H, H_4, $J_{3-4} = J_{4-5} = 9.4$ Hz), 2.39 (m, 2H, $-COCH_2-$), 1.62 (m, 2H, $-CH_2-$), 1.35 (m, 2H, $-CH_2-$), 0.92 (t, 3H, $-CH_3$, $J = 7.5$ Hz). ^{13}C NMR (100.6 MHz, D_2O): 179.4, 76.5, 73.0, 72.7, 69.4, 69.3, 60.5, 35.3, 27.5, 21.5, 13.0.

Synthesis of N^{γ}-(α-D-Glucopyranosyl)-L-asparagine-*O*-methyl Ester (19g). A solution of the substrate **11g** (20 mg, 0.025 mmol) in 85:10:5 DMA/AcOH/H_2O (2.5 mL, 0.01 M) was prepared. The catalyst (10 wt % Pd−C) was added, and the mixture was placed under an atmosphere of hydrogen (3 bar). The mixture was stirred at room temperature for 48 h, and the reaction was monitored by TLC (9:1 $CHCl_3$/MeOH and 60:35:5 $CHCl_3$/MeOH/H_2O). The catalyst was then filtered on a Celite pad and washed with MeOH and water. The solvent was then removed under reduced pressure. Quantitative yield. ^1H NMR (400 MHz, CD_3OD): 5.47 (d, 1H, H_1, $J_{1-2} = 4.3$ Hz), 3.96 (m, 1H, C*H*), 3.73 (s, 3H, $COOCH_3$), 3.72−3.68 (m, 1H, H_3 or H_4), 3.63−3.56 (m, 3H H_2, H_6, and H_3 or H_4), 3.37 (m, 1H, H_5), 3.27−3.22 (m, 1H, $H_{6'}$), 2.89 (m, 1H, $-CH_2-$CH), 2.81 (m, 1H, $-CH_2-$CH). ^{13}C NMR (100.6 MHz, CD_3OD, HETCOR): 78.2, 75.1, 74.7, 71.7, 62.8, 62.7, 53.2, 51.6, 38.5.

Synthesis of N^{α}-*t*-Butoxycarbonyl-N^{γ}-(α-D-glucopyranosyl)-L-asparagine (19h). A solution of the substrate **11h** (28 mg, 0.035 mmol) in 85:10:5 DMA/AcOH/H_2O (3.5 mL, 0.01 M) was prepared. The catalyst (10 wt % Pd−C) was added, and the mixture was placed under an atmosphere of hydrogen (3 bar). The mixture was stirred at room temperature for 24 h, and the reaction was monitored by TLC (6:4 toluene/AcOEt). The catalyst was then filtered on a Celite pad and washed with MeOH and water. The solvent was then removed under reduced pressure. Quantitative yield. ^1H NMR (400 MHz, CD_3OD): 5.53 (d, 1H, H_1, $J_{1-2} = 4.4$ Hz), 4.37 (m, 1H, C*H*), 3.81 (m, 1H, H_6), 3.74−3.61 (m, 3H), 3.49 (m, 1H), 3.34 (m, 1H), 2.86−2.79 (m, 2H, $-CH_2-$CH), 2.88−2.77 (m, 2H, $-CH_2-$CH), 1.45 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (100.6 MHz, CD_3OD, HETCOR): 77.0, 73.3, 13.0, 70.2, 70.1, 61.3, 51.8, 3, 27.4.

Synthesis of N^{α}-Acetyl-N^{γ}-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-L-asparagine-*O*-methyl Ester (21g). Acetic anhydride (35 μL, 0.36 mmol, 15 mol equiv) and a catalytic amount of *N*,*N*-(dimethylamino)pyridine were added, at room temperature, to a solution of **19g** (7.5 mg, 0.024 mmol, 1 mol equiv) in dry pyridine (5.7 mL, 0.15 M). The solution was stirred for 24 h and then was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 and washed with 5% aqueous HCl, 5% aqueous $NaHCO_3$, and water. The organic layer was dried over Na_2SO_4 and concentrated to give the product. Yield = 70%. ^1H NMR (400 MHz, $CDCl_3$): 7.27 (d, 1H, N*H*, $J = 7.5$ Hz), 6.79 (d, 1H, N*H*, $J = 7.5$ Hz), 5.86 (dd, 1H, H_1, $J_{1-2} = 5.4$ Hz, $J_{1-NH} = 8.1$ Hz), 5.39 (dd, 1H, H_3, $J_{2-3} = 10.1$ Hz, $J_{3-4} = 9.6$ Hz), 5.16 (dd, 1H, H_2, $J_{1-2} = 5.4$ Hz, $J_{2-3} = 10.1$ Hz), 5.08 (apparent triplet, 1H, H_4, $J_{3-4} = J_{4-5} = 9.6$ Hz), 4.86−4.80 (m, 1H, $-CHCOOCH_3$), 4.29 (dd, 1H, H_6, $J_{5-6} = 4.3$ Hz, $J_{6-6'} = 12.3$ Hz), 4.07 (dd, 1H, $H_{6'}$, $J_{5-6'} = 2.5$ Hz, $J_{6-6'} = 12.3$ Hz), 3.98−3.92 (m, 1H, H_5), 3.78 (s, 3H, $COOCH_3$), 2.99 (dd, 1H, $-CH_2-$CH, $J = 4.9$, 15.9 Hz), 2.88 (dd, 1H, $-CH_2-$CH, $J = 4.4$, 15.9 Hz), 2.09, 2.05, 2.04, 2.01 (4s, 12H, 4 × $-COCH_3$). ^{13}C NMR (100.6 MHz, $CDCl_3$): 171.2, 170.9, 170.8, 170.4, 170.3, 169.3, 169.1, 74.2, 70.1, 68.6, 68.29, 68.3, 61.8, 52.9, 49.1, 37.9, 23.1, 20.7, 20.6, 20.5. ESI-MS: 541.1 ($M + Na^+$). HRMS (ESI): calculated for $C_{21}H_{30}N_2O_{13}$ $[M + Na]^+$, 541.16401; found $[M + Na]^+$, 541.16363. $[\alpha]^{25}_D = +86.6$ ($c = 0.3$, $CHCl_3$).

Synthesis of *N*-Acetyl-2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosylamine (13a). A solution of the azide **1β** (21.8 mg, 0.058 mmol, 1 mol equiv) and of the phosphine **4a** (22.3 mg, 0.07 mmol, 1.2 mol equiv) in $CHCl_3$ (580 μL, 0.1 M) was prepared at room temperature and under argon. The solution was heated at 70 °C and stirred for 24 h. Then AcOEt was added, and the solution was washed with water. The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The product was purified by flash chromatography using 8:2 toluene/acetone as the eluent. Yield = 81%. ^1H NMR (400 MHz, $CDCl_3$): 6.27 (d, 1H, NH, $J_{1-NH} = 9.5$ Hz), 5.29 (apparent triplet, 1H, H_3, $J_{2-3} = J_{3-4} = 9.5$ Hz), 5.22 (apparent triplet, 1H, H_1, $J_{1-2} = J_{1-NH} = 9.5$ Hz), 5.04 (apparent triplet, 1H, H_4, $J_{3-4} = J_{4-5} = 9.5$ Hz), 4.89 (apparent triplet, 1H, H_2, $J_{1-2} = J_{2-3} = 9.5$ Hz), 4.29 (dd, 1H, H_6, $J_{5-6} = 4.4$ Hz, $J_{6-6'} = 12.5$ Hz), 4.06 (dd, 1H, $H_{6'}$, $J_{5-6'} = 2.2$ Hz, $J_{6-6'} = 12.5$ Hz), 3.80 (ddd, 1H, H_5, $J_{5-6} = 4.4$ Hz, $J_{5-6'} = 2.2$ Hz, $J_{4-5} = 9.5$ Hz), 2.09, 2.07, 2.05, 2.03, 1.99 (5s, 15H, 5 × $-COCH_3$).

General Procedure for the Synthesis of Glycosyl Amides 13g and 14g. A solution of the phosphine **11g** (1.2 mol equiv) in DMA was added, at room temperature and under argon, to a solution of the azide **1*β*** or **8*β*** (1 mol equiv) in DMA (0.1 M). The solution was heated to 70 °C and stirred for 4 h. The disappearance of the starting material was monitored by TLC. After 4 h water (44 μL) was added, and the mixture was stirred for an additional 18 h at the same temperature. The solvent was evaporated under reduced pressure, and the crude was purified by flash chromatography.

N^{α}-Carbobenzyloxy-N^{γ}-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)-L-asparagine-*O*-methyl Ester (13g). Flash chromatography using 6:4 toluene/AcOEt; yield = 69%. ^1H NMR (400 MHz, $CDCl_3$): 7.42−7.33 (m, 5H, aromatics), 6.35 (d, 1H, NH, $J_{1-NH} = 9.0$ Hz), 5.89 (d, 1H, NH, $J_{1-NH} = 8.6$ Hz), 5.22 (apparent triplet, 1H, H_3, $J_{2-3} = J_{3-4} = 9.5$ Hz), 5.16 (apparent triplet, 1H, H_1, $J_{1-2} = J_{2-3} = 9.4$ Hz), 5.05 (m, 2H, $-CH_2Ph$), 4.98 (apparent triplet, 1H, H_4, $J_{3-4} = J_{4-5} = 9.5$ Hz), 4.83 (apparent triplet, 1H, H_2, $J_{1-2} = J_{2-3} = 9.5$ Hz), 4.54 (m, 1H, C*H*), 4.21 (dd, 1H, H_6, $J_{5-6} = 4.3$ Hz, $J_{6-6'} = 12.5$ Hz), 3.99 (dd, 1H, $H_{6'}$, $J_{5-6'} = 1.5$ Hz, $J_{6-6'} = 12.5$ Hz), 3.68 (m, 1H, H_5), 3.66 (s, 3H, COOMe), 2.81 (dd, 1H, CH_2, $J = 16.2$ Hz, $J = 3.7$ Hz), 2.63 (dd, 1H, CH_2, $J = 16.2$ Hz, $J = 3.9$ Hz), 2.11, 2.10, 2.07, 2.06 (4s, 12H, 4 × $-COCH_3$). ^{13}C NMR (100.6 MHz, $CDCl_3$): 171.4, 171.2, 170.6, 169.8, 169.5, 129.0, 128.8, 128.7, 128.2, 128.0, 78.1, 73.8, 72.6, 70.6, 68.1, 67.1, 61.6, 52.7, 50.4, 37.8, 20.7, 20.6. ESI-MS: 611.0 ($M + H^+$), 633.1 ($M + Na^+$). HRMS (ESI): calculated for $C_{27}H_{34}N_2O_{14}$ $[M + Na]^+$, 633.19022; found $[M + Na]^+$, 633.18914. $[\alpha]^{25}_D = +19.4$ ($c = 1.0$, $CHCl_3$).

N^{α}-Carbonzyloxy-N^{γ}-(3,4,6-tri-*O*-acetyl-2-*N*-acetyl-2-deoxy-*β*-D-glucopyranosyl)-L-asparagine-*O*-methyl Ester (14g). Flash chromatography: 98:2 $CHCl_3$/MeOH; yield = 50%. ^1H NMR (400 MHz, $CDCl_3$): 7.40−7.30 (m, 5H, aromatics), 7.12 (d, 1H, NH, $J_{1-NH} = 8.3$ Hz), 6.06 (d, 1H, NH, $J_{2-NH} = 8.0$ Hz), 6.00 (d, 1H, NH, $J_{CH-NH} = 8.6$ Hz), 5.16−5.11 (m, 3H, H_4 and $-CH_2Ph$), 5.05 (apparent triplet, 2H, H_1 and H_3, $J_{1-2} = J_{1-NH} = J_{2-3} = J_{3-4} = 9.6$ Hz), 4.64 (m, 1H, C*H*), 4.30 (dd, 1H, H_6, $J_{5-6} = 4.1$ Hz, $J_{6-6'} = 12.7$ Hz), 4.16−4.07 (dd, 1H, $H_{6'}$ and H_2), 3.77−3.70 (m, 1H, H_5), 3.74 (s, 3H, COOMe), 2.89 (dd, 1H, CH_2, $J = 16.2$ Hz, $J = 3.9$ Hz), 2.73 (dd, 1H, CH_2, $J = 16.2$ Hz, $J = 4.0$ Hz), 2.09, 2.08, 2.05, 1.98 (4s, 12H, 4 × $-COCH_3$). ^{13}C NMR (100.6 MHz, $CDCl_3$): 172.4, 172.0, 171.5, 171.0, 170.6, 169.2, 128.5, 128.2, 128.1, 80.4, 73.6, 72.8, 68.1, 67.1, 61.7, 53.5, 52.7, 50.4, 37.7, 23.0, 20.7, 20.6. ESI-MS: 632.2 ($M + Na^+$). HRMS (ESI): calculated for $C_{27}H_{35}N_3O_{13}$ $[M + Na]^+$, 632.20621; found $[M + Na]^+$, 623.20531. $[\alpha]^{25}_D = +7.25$ ($c = 0.5$, $CHCl_3$).

Iminophosphorane 15. ^{1}H NMR (400 MHz, $CDCl_3$): 7.78−7.25 (m, 19H, aromatics), 5.94 (dd, 1H, H_3, $J_{2-3} = J_{3-4} = 9.6$ Hz), 5.75 (d, 1H, NH, $J = 8.9$ Hz), 5.29 (dd, 1H, H_1, $J_{1-2} = 3.7$ Hz, $J_{1-P} = 22.6$ Hz), 5.16 (s, 2H, $-CH_2Ph$), 5.09 (apparent triplet, 1H, H_4, $J_{3-4} = J_{4-5} = 9.6$ Hz), 4.85 (dt, 1H, H_2, $J_{1-2} = J_{2-P} = 3.7$ Hz, $J_{2-3} = 9.6$ Hz), 4.61 (m, 1H, H_5), 4.47 (m, 1H, −C*H*NH), 4.19 (dd, 1H, H_6, $J_{5-6} = 3.9$ Hz, $J_{6-6'} = 12.0$ Hz), 3.84 (m, 1H, $H_{6'}$), 3.73 (s, 3H, $-COOCH_3$), 2.52 (dd, 1H, CH_2, $J = 17.4$ Hz, $J = 5.9$ Hz), 2.03 (m, 1H, CH_2), 2.09, 2.04, 2.02, 1.76 (4s, 12H, 4 × $-COCH_3$). ^{13}C NMR (100.6 MHz, $CDCl_3$, HETCOR): 73.8, 71.7, 69.1, 67.2, 65.7, 62.8, 52.7, 50.4, 35.7, 21.6, 20.9, 20.8.

Synthesis of 1-*N*-Pentanedioic Acid 2-*N*-Phthalimido-2-deoxy-3,4,6-tri-*O*-acetyl-*β*-D-glucopyranosyl Amide Methyl Ester (16f). A solution of the phosphine **4f** (11.3 mg, 0.029 mmol, 1.2 mol equiv) in DMF was added, at room temperature and under argon, to a solution of the azide **9α** (11.1 mg, 0.024 mmol, 1 mol equiv) in DMF (240 μL, 0.1 M). The solution was heated to 70 °C and stirred for 20 h. The disappearance of the starting material was monitored by TLC (1:1 hexane/AcOEt). After 20 h water (24 μL) was added, and the mixture was stirred for an additional 20 h at the same temperature. The solvent was evaporated under reduced pressure, and the crude was purified by flash chromatography using 65:35 hexane/AcOEt as the eluent. Yield = 58%. ^{1}H NMR (400 MHz, $CDCl_3$): 7.90−7.80 (m, 2H, aromatics), 7.77−7.72 (m, 2H, aromatics), 6.08 (d, 1H, NH, $J_{1-NH} = 8.3$ Hz), 6.05 (dd, 1H, H_1, $J_{1-2} = 9.9$ Hz, $J_{1-NH} = 8.3$ Hz), 6.03 (dd, 1H, H_3, $J_{2-3} = 10.0$ Hz, $J_{3-4} = 9.5$ Hz), 5.18 (apparent triplet, 1H, H_4, $J_{3-4} = J_{4-5} = 9.5$ Hz), 4.39 (dd, 1H, H_6, $J_{5-6} = 4.3$ Hz, $J_{6-6'} = 12.4$ Hz), 4.29 (dd, 1H, H_2, $J_{1-2} = 9.9$ Hz, $J_{2-3} = 10.0$ Hz), 4.17−4.11 (m, 1H, $H_{6'}$), 4.04−3.99 (m, 1H, H_5), 3.62 (s, 3H, $COOCOOCH_3$), 2.23−2.08 (m, 4H, $-COCH_2$), 1.78 (m, 2H, $-COCH_2$, $J = 7.5$ Hz), 2.13, 2.05, 1.91 (3s, 9H, 3 × $-COCH_3$). ^{13}C NMR (100.6 MHz, $CDCl_3$): 172.2, 170.7, 169.9, 169.7, 134.7, 134.3, 124.1, 123.5, 75.9, 73.7, 70.6, 68.6, 61.9, 54.2, 51.5, 35.1, 32.6, 29.7, 20.7, 20.6, 20.4, 20.1. HRMS (ESI): calculated for $C_{26}H_{30}N_2O_{12}$ $[M + H]^+$, 563.18715; found $[M + H]^+$, 563.18765.

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Supporting Information Available: Procedures for the synthesis of glycosyl azides **1α**, **1*β***, **5α**, **5*β***, **6α**, **6*β***, **7α**, **8*β***, and **9α**, synthesis and characterization of the functionalized phosphines **4**, NOE contacts and coupling constants of the α-acetamides **18a**−**20a**, ^{1}H, ^{13}C, and ^{31}P NMR spectra for compounds **4a**−**4i**, **11f**−**11i**, **12c**, **18a**, **19a**, **20a**, **19b**, **19g**, **19h**, **21g**, **13g**, **14g**, and **16f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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