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Stereoselective Synthesis of α- and β-Glycofuranosyl Amides by Traceless Ligation of Glycofuranosyl Azides

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Abstract: A highly stereoselective synthesis of α- or β-glycofuranosyl amides based on the traceless Staudinger ligation of glycofuranosyl azides of the *galacto*, *ribo*, and *arabino* series with 2-diphenylphosphanyl-phenyl esters has been developed. Both α- and β-isomers can be obtained with excellent selectivity from a common, easily available precursor. The process does not depend on the anomeric configuration of the starting azide but appears to be controlled by the C2 configuration and by the protection/deprotection state of the substrates. A mechanistic interpretation of the results, supported by ^{31}P NMR experiments, is offered and merged with our previous mechanistic analysis of pyranosyl azide ligation reactions.

Keywords: azides · carbohydrates · glycomimetics · neo-glycoconjugates · Staudinger ligation · stereoselective synthesis

Introduction

N-Glycosyl amides and their structural mimics are currently under intense scrutiny as potential effectors of carbohydrate-binding proteins, useful both as potential drugs and for clarifying the biological roles of oligosaccharides.[1] A major synthetic effort is under way to synthesize so-called "neo-glycoconjugates", in which a sugar ring is connected through a nitrogen atom to a carbon chain, often to a natural amino acid, using an unnatural linkage.[2–11] Natural *N*-linked glycopeptides are almost invariably β-linked.[12] The unnatural, α-linked isomers have attracted some attention as glycopeptide mimics, since they may be stable to hydrolytic enzymes and may be used for in vivo applications.[11] It has been shown that the stereochemistry of the carbohydrate–peptide linkage has critical and unique conformational effects on glycopeptide structures.[13] Additionally, we have shown that α-*N*-linked glycopyranosyl amides in the *gluco*, *galacto*, and *fuco* series maintain the normal pyranose conformation of the monosaccharide, which represents an important feature for their use as sugar mimics.[11a] Indeed, a small group of α-fucosyl amides have shown good affinity for the carbohydrate recognition domain (CRD) of fucose-binding proteins, such as DC-SIGN[14] and PA-II lectin.[15]

The most widely employed method for the synthesis of glycosyl amides is the condensation of carboxylic acid derivatives with protected or unprotected glycosylamines.[16] The latter may also be obtained by reduction of glycosyl azides.[17–20] Because glycopyranosylamines rapidly equilibrate to the most stable β-anomer, all of the approaches that make use of isolated amine intermediates afford β-glycopyranosyl amides. An alternative methodology attempts to avoid anomeric equilibration by reducing glycosyl azides in the presence of acylating agents, most often employing phosphines for the reduction step (Staudinger reduction).[21–26] However, Staudinger intermediates (aza-ylides or iminophosphoranes) are also subject to anomeric isomerization, which for glycopyranoses is biased toward the β-anomers. Thus, while β-glycosyl amides can be prepared, anomerization remains a significant problem in the synthesis of the α-anomers.

A limited number of methods are available for the synthesis of α-glycosyl amides. Most of them require two steps and have been described for a limited number of substrates.[10,27,28] Our group has reported a method based on the traceless Staudinger ligation of glycosyl azides,[11a,28,29] using functionalized phosphines **1** (2-diphenylphosphanyl-phenyl esters) originally described by Bertozzi[30] and Kiessling.[31] The phosphines used are modified to include an acylating agent, which in **1** is a phenolic ester. Reduction of the starting azide is followed by fast intramolecular trapping of the reduction intermediates, which results in direct formation of an amide bond. We have shown that, depending on the sugar protecting groups, this approach can prevent epimerization of glycopyranoses and allows retention of configuration at the anomeric carbon (Scheme 1).[11,28] In particular, we have identified reaction conditions that allow the clean and stereoconservative ligation of unprotected glycopyranosyl azides in good to moderate yields, affording α- or β-glycopyranosyl amides depending on the configuration of

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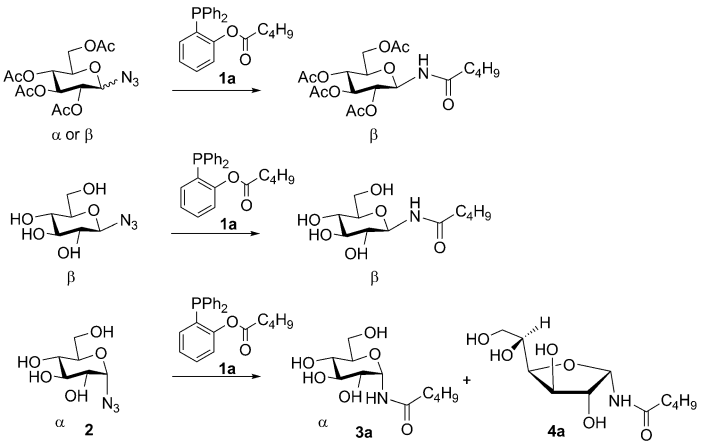
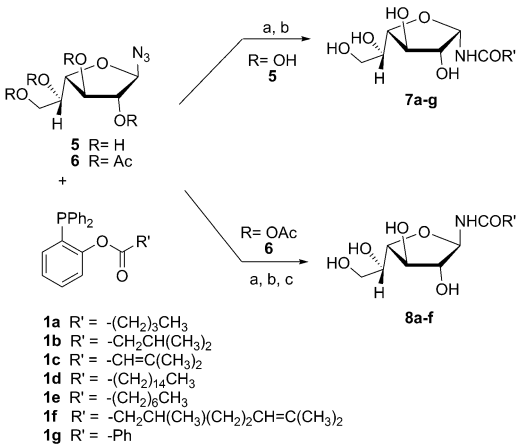


Scheme 1. Staudinger ligation of gluco-pyranosyl azides with **1a** (from ref. [11a]).



Scheme 2. Stereoselective synthesis of α- and β-Gal*f* amides **7a–g** and **8a–f** (from ref. [39]). Reagents and conditions: a) 70 °C, 4 h, 98:2 *N*,*N*-dimethylacetamide/1,3-dimethyltetrahydro-2(1*H*)pyrimidinone (DMA/DMPU); b) H_2O, 2 h, 70 °C; c) MeO^-Na^+ (0.05 M), MeOH.

the starting material (Scheme 1).[29] Starting from α-glycopyranosyl azides, a by-product of this reaction is the glycofuranosyl isomer derived from a ring-contraction process. For instance, treatment of α-glucopyranosyl azide **2** with phosphine **1a** afforded α-*N*-valeroyl-glucopyranosyl amide **3a** and α-*N*-valeroyl-glucofuranosyl amide **4a**. Their ratio depended mainly on the reaction temperature, with the amount of the furanose form increasing at higher temperatures.[29] Although the amount of furanose product could be kept below 5–10%, this finding drew our attention towards this atypical class of compounds. In particular, the furanose form of D-glucose is known to be unstable[32] and it is rarely isolated, usually as a bis-acetonide[33] or a boronate.[34]

On the other hand, other hexofuranoses play important roles in biological systems.[35] For instance, galactofuranosyl (Gal*f*) residues are constituents of the galactan polymer in mycobacterial cell walls. The Gal*f* units are created by bacterial mutases, which convert UDP-galactopyranose into UDP-galactofuranose, and are essential for the viability of mycobacteria.[36] Mammals do not synthesize hexofuranoses, and therefore molecules of this class are emerging as potential candidates for therapeutic development. UDP-galactopyranose mutase inhibitors have been reported and shown to block the growth of *Mycobacterium tuberculosis*.[37] Simple galactofuranosyl and arabinofuranosyl derivatives at low micromolar concentrations have been shown to inhibit bacterial growth by a mechanism that has not yet been fully elucidated.[38] We have initially focused our attention on galactofuranosyl amides and have recently reported preliminary results showing that α- or β-Gal*f* amides **7a–g** and **8a–f** can be synthesized with high stereoselectivity by traceless Staudinger ligation starting from unprotected β-galactofuranosyl azide **5** or tetra-*O*-acetyl-β-galactofuranosyl azide **6**, respectively (Scheme 2).[39]

These results offer a simple, stereodivergent way of synthesizing glycofuranosyl amides of either anomeric configuration starting from the same azide and controlling the process through the absence/presence of acetyl protecting groups. At first sight, however, these results are intriguingly at odds with those obtained with α-pyranosyl azides, which undergo ligation without inversion of configuration when deprotected and anomerize to β-amides when acetylated (Scheme 1). Therefore, after our preliminary report, we focused on examining the full scope of this reaction and on understanding how its stereochemical course is determined. Our results are reported herein. We first ascertained that the stereochemical outcome of the process does not depend on the anomeric configuration of the starting azide by synthesizing the (previously unknown) α-epimer of **5** and studying its ligation with **1a**. We then examined the ligation of *ribo*- and *arabino*-furanosyl azides, which allowed us to establish that the stereochemistry of the reaction is controlled by the C2 configuration of the sugar. Finally, based on these results and on ^{31}P NMR spectroscopic data, we suggest a mechanistic interpretation of the process and merge it with our previous mechanistic analysis of pyranosyl azide ligation reactions.

Results

Synthesis of starting materials: The structures of the glycofuranosyl azides **5**, **6**, and **9**–**14** used in this work are collected in Figure 1. The 1,2-*trans*-furanosyl azides in the *galacto* (**6**), *ribo* (**10**[40]), and *arabino* (**12**) series were synthesized starting from the corresponding acetates[41,42] under Paulsen's conditions ($TMSN_3/SnCl_4$). The anomeric configuration of the compounds was confirmed by NOE experiments ($CDCl_3$), which showed correlations of H1 with H3 in **5**, H4 in **10**, and H5 in **12**. Zemplen deacetylation (cat. MeONa in MeOH) afforded the unprotected β-galactofuranosyl azide **5**, β-ribofuranosyl azide **9**, and α-arabinofuranosyl **11** without loss of configurational integrity.

To the best of our knowledge, 1,2-*cis* α-galactofuranosyl azides in unprotected (**13**) and tetra-*O*-acetylated form (**14**) have never been described before. They were prepared from

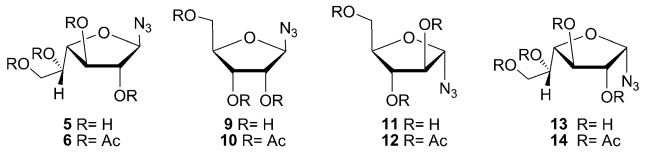
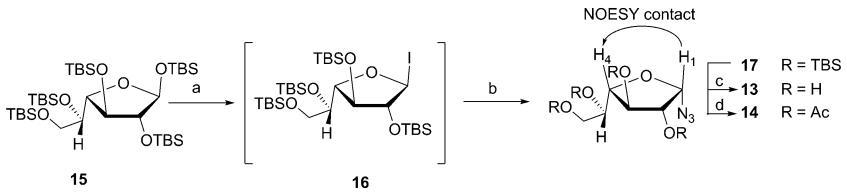


Figure 1. Furanosyl azides used in this work.

1,2,3,5,6-penta-*O*-*tert*-butyldimethylsilyl-β-galactofuranose **15** (Scheme 3), which was recently described by Baldoni and Marino.[43] This was transformed into iodide **16**[43] by reaction with trimethylsilyl iodide (TMSI; 1.2 equiv) in anhydrous CH_2Cl_2 at 0 °C for 30 min. When TLC showed complete consumption of **15**, tetrabutylammonium azide (nBu_4NN_3) was added and the mixture was stirred overnight at room temperature. The reaction afforded the 2,3,4,6-tetra-*O*-*tert*-butyldimethylsilyl-α-galactofuranosyl azide **17** in good yield and with high stereoselectivity, the anomeric configuration of which was confirmed by the observation of a NOESY correlation between H1 and H4 (Scheme 3). Removal of the TBS groups from **17** was accomplished with tetrabutylammonium fluoride (TBAF) in THF and afforded unprotected α-galactofuranosyl azide **13**. The anomeric configuration of **13** was also confirmed by NOESY experiments, which showed a clear correlation between protons H1 and H4, and by the chemical shift for C4 of 84.5 ppm, which is diagnostic of the furanose form. Acetylation of **13** (Ac_2O in pyridine, Scheme 3) afforded 2,3,5,6-tetra-*O*-acetyl-α-galactofuranosyl azide **14**. A NOESY contact between H1 and H4 ($CDCl_3$) was also observed in this compound.



Scheme 3. Synthesis of α-D-Gal*f* azides **13** and **14** from galactofuranosyl iodide **16**. Reagents and conditions: a) TMSI, CH_2Cl_2, 0 °C, 30 min (see ref. [42]); nBu_4NN_3, diisopropylethylamine (DIPEA); c) TBAF; d) Ac_2O/pyridine. TBS = *tert*-butyldimethylsilyl.

For comparison purposes and to fully characterize the ligation products, the corresponding β-D-ribopyranosyl azides[44] **18** and **19** and β-L-arabinopyranosyl azides[45] **20** and **21** (Figure 2) were also synthesized (from the corresponding acetates under Paulsen's conditions) and reacted with **1**. The β-configuration of **18**–**21** was supported by the value of the vicinal coupling constant of the anomeric proton ($J_{1,2}$ = 8 Hz) and their pyranose structure by the chemical shift for C4 (δ = 67.8 ppm).

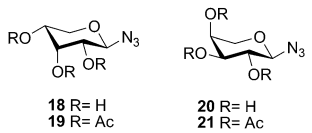


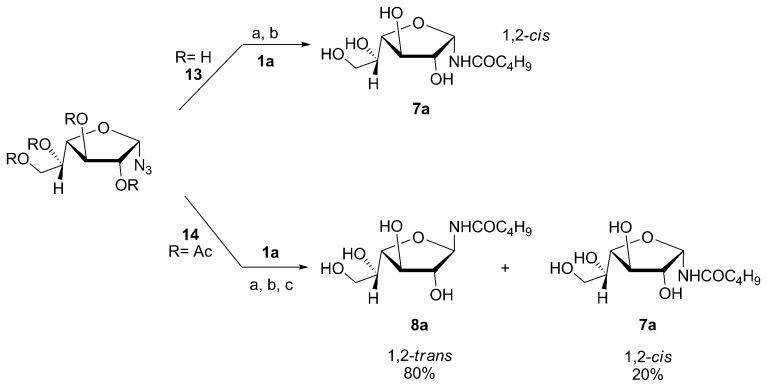
Figure 2. Pentapyranosyl azides (β-D-ribopyranosyl azides **18** and **19** and β-L-arabinopyranosyl azides **20** and **21**) used for comparison purposes.

2-Diphenylphosphanyl-phenyl esters **1** were prepared as previously described[11,39] by acylation of *o*-diphenylphosphinophenol.[46]

Ligation reactions: All ligation reactions were performed using the protocol reported for β-galactofuranosyl azides **5** and **6** in our preliminary communication.[39] In brief, a mixture of unprotected azide and phosphine **1** (Scheme 2) in DMA/DMPU (98:2) was stirred for 4 h at 70 °C, then water was added and, after an additional 2 h at the same temperature, the solvent was evaporated and the product was isolated by extraction with water. Diastereomeric ratios were determined for the crude products by ^{1}H NMR (CD_3OD) and the resulting amides were purified by flash chromatography. The same conditions were adopted for the ligation of tetra-*O*-acetyl azides. Again, the crude reaction mixtures were analyzed by ^{1}H NMR ($CDCl_3$) to establish the isomer distribution, but, to simplify purification of the reaction products from phosphine oxide, the tetra-*O*-acetyl amides were not isolated but were deacetylated to afford the corresponding unprotected amides. The latter were finally isolated and purified by flash chromatography on silica gel. The deprotection step was found to be critical to preserve configurational integrity at the anomeric carbon. While a 0.05 M solution of MeONa in MeOH and short contact times (45 min) could be used successfully, more concentrated (0.1 M) solutions caused anomeric epimerization. This process most probably occurs by MeONa-induced deprotonation of the amide nitrogen (see below) and can be suppressed by using a milder base for the deprotection. No epimerization was observed using $MeNH_2$ in EtOH.[47]

The reactions of β-galactofuranosyl azides **5** and **6** were studied first (Scheme 2). The structures and anomeric configurations of **7a** and **8a** were determined by NMR, as described above for the starting azides and fully detailed in the preliminary communication.[39] In all cases, β-anomers were obtained from tetra-*O*-acetyl azide **6**, with retention of the anomeric configuration, whereas α-anomers were obtained from unprotected azide **5**, which appears to undergo inversion of its anomeric configuration during the reaction. This anomeric inversion must derive from a ring-opening process after the azide reduction step. We will discuss our mechanistic hypothesis for this intriguing process in the following section. For the moment, we note only that ring-opening should actually be favored for the *O*-acetylated substrate, thus we initially found these results rather puzzling.

In an effort to better correlate the steric course of the reaction with the structure of the starting azides, we submitted



Scheme 4. Ligation of α-galactofuranosyl azides **13** and **14** with phosphine **1a**. Reagents and conditions: a) 70 °C, 4 h, DMA/DMPU 98:2; b) H_2O, 2 h, 70 °C; c) MeO^-Na^+ (0.05 M), MeOH.

the α-galactofuranosyl azides **13** and **14** to Staudinger ligation with **1a** (Scheme 4). Surprisingly, the unprotected azide **13** underwent a stereoconservative process yielding the α-amide **7a**, whereas inversion of the anomeric configuration was observed for the tetra-*O*-acetyl substrate **14**. In other words, regardless of their anomeric configurations, both the α- and β-unprotected galactofuranosyl azides **5** and **13** gave α-amides (1,2-*cis*), whereas both the α- and β-tetra-*O*-acetyl-galactofuranosyl azides **6** and **14** gave β-amides (1,2-*trans*).

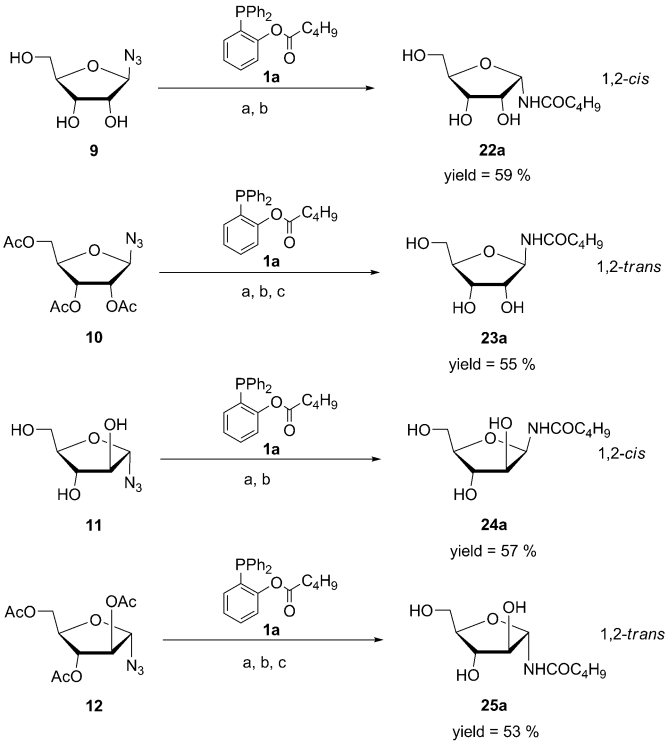
To further explore the scope and mechanism of this reaction, the ribofuranosyl azides **9** and **10** and the arabinofuranosyl azides **11** and **12** (Scheme 5) were subjected to traceless ligation with compound **1a** under the same conditions as used above. All of these azides feature a 1,2-*trans* configuration, with opposite configuration at C2 in the *ribo* and *arabino* series. These reactions also afforded 1,2-*cis* amides (**22a** and **24a**) from the unprotected azides (**9** and **11**) and 1,2-*trans* amides (**23a** and **25a**) from the corresponding *O*-acetyl compounds (**10** and **12**) (Scheme 5).[48] Thus, these experiments established that the stereochemical outcome of the process is controlled by the C2 configuration, as well as by the protection state of the monosaccharide.

To fully confirm the characterization of **22a**–**25a**, the corresponding pyranosyl azides **18**–**21** were also subjected to ligation with **1a** (Scheme 6). As expected for β-pyranosyl azides,[11a] β-amides (**26a** and **27a**) were obtained in all cases, as established by the vicinal coupling constant of the anomeric protons (**26a** $J_{1,2}=8$ Hz; **27a** $J_{1,2}=8.8$ Hz) and the chemical shift of C4 ($\delta=68.8$ ppm).

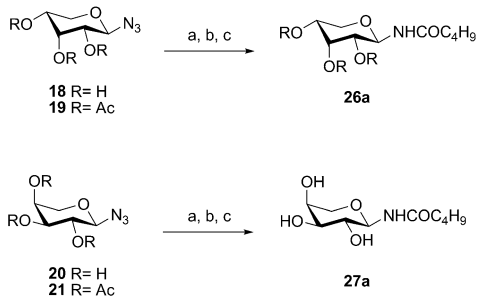
The studies detailed above allowed us to fully describe the steric course of the ligation of glycofuranosyl azides and to compare it with the available data for the same reaction of the pyranose isomers. In the pyranose series (Scheme 1 and Scheme 6), β-azides always give β-amides irrespective of the protection state of the sugar hydroxy groups; α-azides undergo inversion of their anomeric configuration if *O*-acetylated and preserve it if unprotected (Scheme 1). In the furanose series (Schemes 2, 4, and 5), irrespective of the anomeric configuration of the starting material, unprotected azides (**5**, **9**, **11**, and **13**) afford amides of 1,2-*cis* configuration, whereas *O*-acetyl-glycofuranosyl azides (**6**, **10**, **12**, and **14**) afford the 1,2-*trans* anomers.

Reaction mechanism

Unprotected furanosyl azides: The ligation of unprotected 1,2-*trans* furanosyl azides **5**, **9**, and **11** with phosphine **1a** afforded glycofuranosyl amides with the opposite 1,2-*cis* anomeric configuration relative to the start-

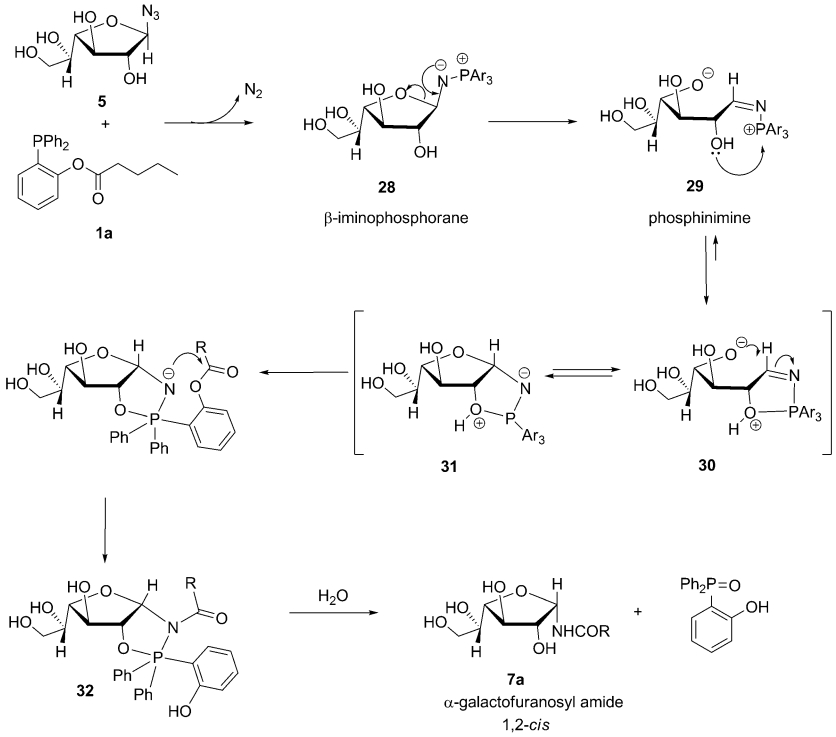


Scheme 5. Staudinger ligation of **1a** with β-ribofuranosyl azides **9** and **10** and α-arabinofuranosyl azides **11** and **12**. Reagents and conditions: a) 70 °C, 4 h, DMA/DMPU 98:2; b) H_2O, 2 h, 70 °C; c) $MeNH_2$ (0.046 M), EtOH.



Scheme 6. Staudinger ligation of β-D-ribo- and β-L-arabinopyranosyl azides with **1a**. Reagents and conditions: a) **1a**, 70 °C, 4 h, DMA/DMPU 98:2; b) H_2O, 2 h, 70 °C; c) MeO^-Na^+ (0.05 M), MeOH.

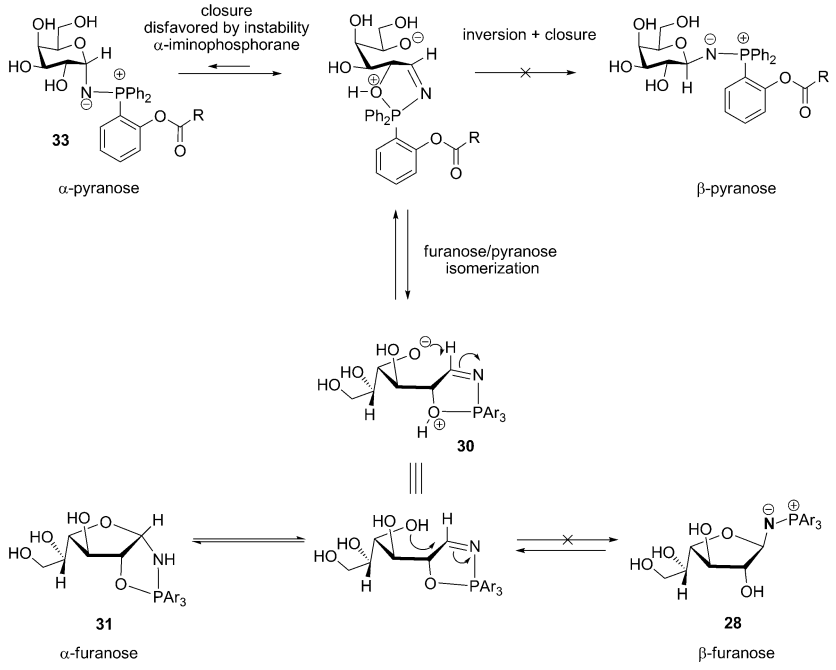
ing azide precursor (Schemes 2 and 5). This anomeric epimerization must derive from a ring-opening process after the azide reduction step. A possible mechanism for the reaction of **1a** with β-galactofuranosyl azide **5** is shown in Scheme 7. Upon azide reduction, iminophosphorane **28** (Scheme 7) is formed, ring-opening of which affords phosphinimine **29**. From this open-chain intermediate, the ring-closure step could be biased by the unprotected hydroxyl group at C2, which can trap the phosphorus atom of **29** as the cyclic oxazaphospholane intermediate **30**, thus enforcing, after ring-closure, formation of the 1,2-*cis* isomer **31**. In other words, the anomeric carbon of the sugar is blocked by chelation of the phosphorus in intermediate **30**, such that only α-amides can be obtained upon ring-closure. Intramolecular acyl transfer then affords **32**, which is finally hydrolyzed to the 1,2-*cis* amide **7a** with overall inversion of the anomeric configuration.



Scheme 7. Proposed mechanism for the formation of 1,2-*cis*-amides from unprotected glycofuranosyl azides.

This proposal implies that ligation of unprotected furanosyl azides, irrespective of the anomeric configuration of the azide, will enforce a 1,2-*cis* configuration in the resulting amides by coordination of the free OH group in the 2-position with the P atom of the iminophosphorane. Thus, the stereochemical course of the reaction is controlled by the C2 configuration of the sugar, which explains the anomerization observed upon reaction of **1a** with unprotected α-arabinofuranosyl azide **11** and β-ribofuranosyl azide **9** (Scheme 5), as well as the *retention* of anomeric configuration observed upon ligation of unprotected α-galactofuranosyl azide **13** (Scheme 4).

Additionally, this mechanistic proposal explains the puzzling observation of a furanose ring-opening event that occurs without causing ring-expansion to the normally favored pyranose structure. Indeed, once oxygen–phosphorus coordination has occurred to give **30**, formation of a 1,2-*cis* sugar ring is enforced. In a pyranose ring, this implies formation of the α-anomer of a pyranosyliminophosphorane (**33**, Scheme 8), which is sterically destabilized. Hence, the process is entirely funneled through the 1,2-*cis* furanose structure, via intermediate **31**.



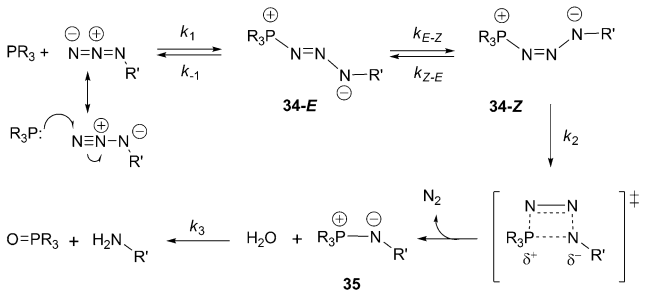
Scheme 8. Furanose-to-pyranose isomerization is disfavored by formation of oxazaphospholane **30**.

O-*Acetyl furanosyl azides*: Given the known propensity of *O*-acetyl glycopyranosyl iminophosphoranes to undergo ring-opening and anomeric equilibration,[11] it was rather surprising to observe a totally stereoconservative process in the ligation of 1,2-*trans O*-acetyl-glycofuranosyl azides, such as **6** (β-tetra-*O*-acetyl-galactofuranosyl azide, Scheme 2) or **10** and **12** (β-tri-*O*-acetyl-ribofuranosyl azide and α-tri-*O*-acetyl-arabinofuranosyl azide, Scheme 5). Literature data indicate small energetic differences for the α- and β-isomers of furanoses[32] and hence ring-opening would be expected to produce a mixture of anomeric amides. For instance, reduction of 1,2-*trans*-β-tri-*O*-benzoyl-ribofuranosyl azide and in situ acylation with DCC and Cbz-glycine was reported to afford a 2:1 mixture of 1,2-*cis*:1,2-*trans* amides.[49] Indeed, ligation of 1,2-*cis* α-tetra-*O*-acetyl-galactofuranosyl azide **14** with **1a** (Scheme 4) affords a 4:1 mixture of β- (1,2-*trans*) and α- (1,2-*cis*) isomeric amides **8a** and **7a**, which must originate from a ring-opening event. The partial inversion of anomeric configuration observed in this reaction strongly suggests that when ring-opening occurs in these furanose substrates, the subsequent ring-closure is biased towards the formation of 1,2-*trans*-amides, presumably for steric reasons, amplified by the steric bulk of the P substituents.

^{31}P NMR spectroscopy: Evidence for the formation of O–P coordination in the ligation of unprotected azides was gathered by ^{31}P NMR spectroscopy in [D_7]DMF. Initial experiments performed using **5** and **1a** were disappointing: disappearance of the phosphine signal at $\delta = -14.9$ ppm was observed, but this was not accompanied by accumulation of the relevant intermediates. Similar observations were reported by Raines et al.[50] and Bertozzi et al.[51] in NMR studies of traceless ligation reactions with different phosphines. However, when galactofuranosyl azide **5** was added to Ph_3P at 70 °C, four new P signals appeared at $\delta = 20.4$, 13.9, −48.3, and −48.5 ppm, all correlated to a proton in the anomeric region of the ^{31}P-^{1}H-HMBC spectrum, and were found to persist for over 1 h, before addition of water transformed all phosphorus intermediates into triphenyl phosphine oxide ($\delta = +26.2$ ppm). The two signals at $\delta =$ 13.9 ppm and 20.4 ppm can be assigned to the β- and α-iminophosphoranes, respectively. The β-signal is formed first and slowly decreases with time, while two new signals appear at $\delta = -48.5$ and −48.3 ppm. These values are consistent with a large upfield shift caused by coordination of the oxygen to the phosphorus atom and can most probably be assigned to two stereoisomers of the postulated oxazaphospholane. On the contrary, when tetra-*O*-acetyl-galactofuranosyl azide **6** was treated with Ph_3P under the same conditions, only the signal of the β-iminophosphorane was observed at $\delta = 12.1$ ppm, together with that of triphenyl phosphine oxide.[52] Thus, these data support the mechanistic hypothesis outlined in Schemes 7 and 8.

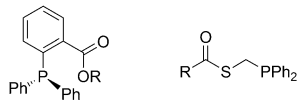
Discussion

The mechanism of the Staudinger reaction has been extensively studied by computational[53–55] and experimental methods.[26b,56] The numbers of intermediates and possible reaction pathways connecting them to each other and to the starting and final products is large and the potential-energy surface is extremely complex. Nucleophilic attack of the phosphine on an azide generates a phosphazide (phosphotriazadiene) intermediate (**34**), which decomposes in a process accelerated by polar solvents, to release N_2 and an iminophosphorane (**35**, Scheme 9).



Scheme 9. Schematic mechanism of the classic Staudinger reaction.

Iminophosphoranes are relatively stable species and have been isolated in a number of instances.[53] In particular, glycosyl iminophosphoranes from *O*-acetyl-protected sugars are rather stable, and many have been isolated and characterized by NMR spectroscopy.[28b,57] The Staudinger ligation of azides with functionalized phosphines has recently been reviewed.[58] Mechanistic investigations of the traceless Staudinger ligation with phosphine **36**[51] and with (diphenylphosphino)methanethiol **37**[50,59] (Figure 3) have been reported.



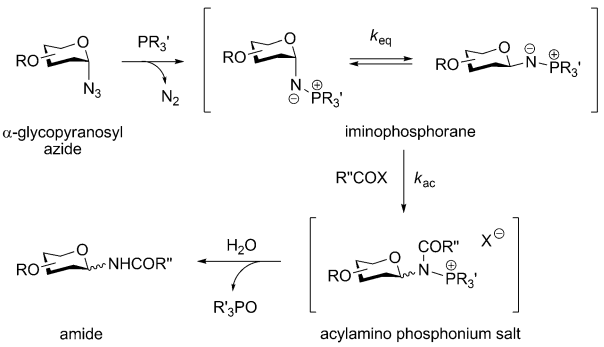
36 37

Figure 3. Phosphines **36** and **37**.

In previous studies in our laboratory, we have examined the stereochemical outcomes of ligations of α-tetra-*O*-benzyl,[11,28] α-tetra-*O*-acetyl,[11] and unprotected[29] α-glycopyranosyl azides with phosphine **1a**, and we proposed some mechanistic hypotheses to interpret the resulting observations. Reduction–acylation of α-tetra-*O*-acetyl-glycopyranosyl azides (Scheme 1) was found to be a non-stereoconservative process and β-glycopyranosyl amides were consistently obtained. These results are in agreement with literature reports obtained by the Kiessling group using dialkylphosphino-(borane)methanethioesters and acetylated sugars.[60]

We speculated that α-tetra-*O*-acetyl-glycopyranosyl iminophosphoranes may be deactivated toward acyl transfer by

the electron-withdrawing effect of acetyl groups, which delocalizes the negative charge on the nitrogen atom and allows anomeric equilibration to occur before the acyl-transfer step (Scheme 10, $k_{eq} > k_{ac}$). For tetra-*O*-benzyl and under intermediates must also undergo a ring-opening process, at least to some extent. This, however, does not lead to α-β equilibration, but rather to ring-contraction, which is most unusual for pyranoses in the *gluco* configuration.

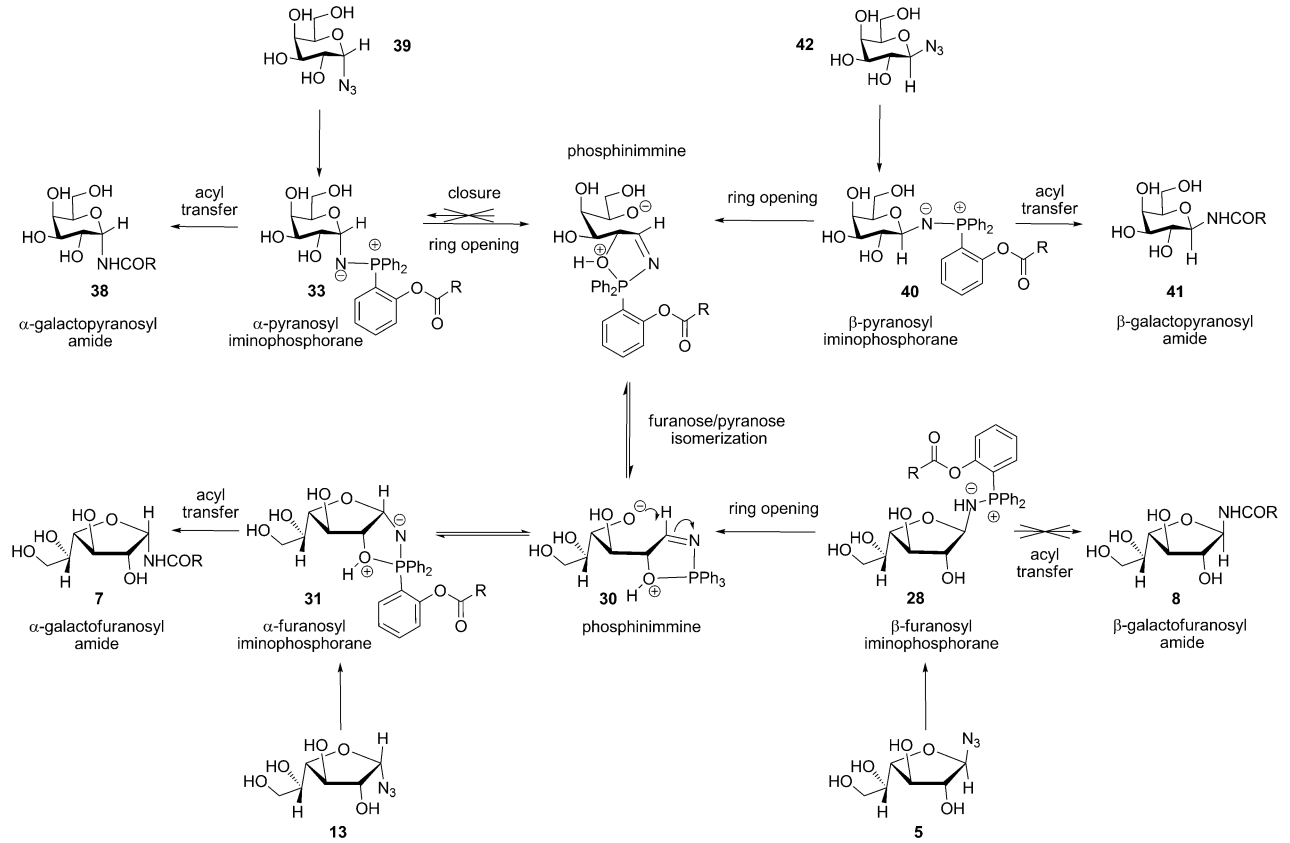


Scheme 10. Anomeric equilibration versus acylation in the Staudinger reduction–acylation of α-glycopyranosyl azides.

protected derivatives (Scheme 1), a more localized negative charge on the anomeric nitrogen leads to faster acyl transfer ($k_{ac} > k_{eq}$) and blocks ring-opening and anomerization. The same explanation may be applied to the formation of α-amides **3a** from unprotected azide **2** (Scheme 1). However, formation of variable quantities of glucofuranosyl amides **4a** upon reaction of **2** suggests that these unprotected Staudinger intermediates must also undergo a ring-opening process, at least to some extent. This, however, does not lead to α-β equilibration, but rather to ring-contraction, which is most unusual for pyranoses in the *gluco* configuration.

Closer examination of the ligation reaction of unprotected furanosyl azides has now revealed a more complex mechanistic picture. First, and perhaps most strikingly, the reactions of pyranosyl and furanosyl azides appear, at first sight, to follow opposite stereochemical pathways. In fact, 1,2-*trans O*-acetyl-furanosyl azides of the *galacto*-, *ribo*-, and *arabino*- series (**6**, **10**, and **12**) do not isomerize upon ligation with **1**, whereas the same furanosyl azides do isomerize when they are unprotected (compounds **5**, **10**, and **12**, respectively). This behavior, exemplified in Scheme 2 for β-galactofuranosyl azides **6** and **5**, is exactly the opposite of that described for pyranoses in Scheme 1.

The mechanistic path proposed in Scheme 7 can be used to reconcile the apparently opposite behaviors of pyranosyl and furanosyl azides in the ligation process. The full mechanistic picture is shown in Scheme 11, using unprotected galactosyl azides **5** and **13** as substrates. The reaction course is dominated by the competition between acyl-transfer and ring-opening processes, as suggested above. However, for unprotected sugars, the behavior of the acyclic intermediate, a phosphinimine, is more complex than previously discussed. In fact, once the phosphinimine is formed, the phosphorus atom is probably trapped by the C2 hydroxy group of the



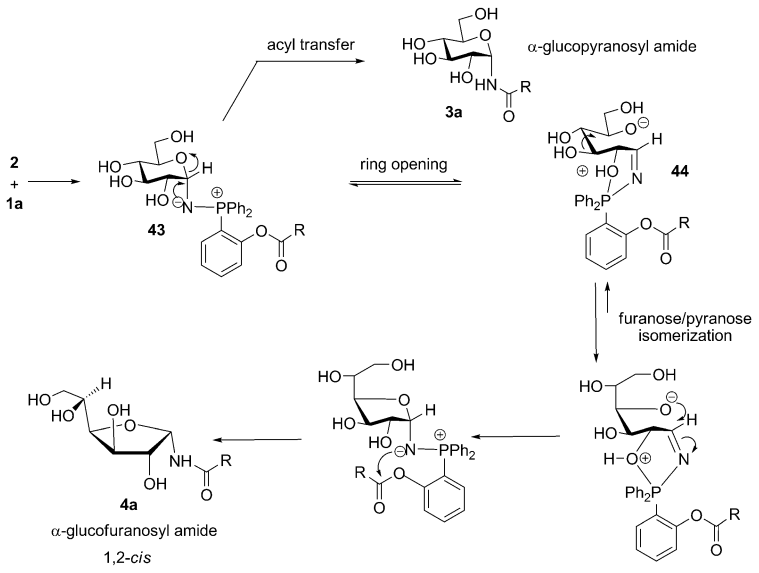
Scheme 11. Full mechanistic pathway for the reaction of unprotected galactosyl azides.

sugar in a five-membered oxazaphospholane ring, exemplified as **30** in Scheme 11. Formation of this cyclic intermediate is supported by the ^{31}P NMR data reported above. Once this cycle is formed, the ring-closure process can no longer lead to reversion to β-isomers of the iminophosphorane and only the left-hand side of Scheme 11 is still available. In particular, **30** can cyclize by attack of O4 at the anomeric carbon to form the α-furanosyl iminophosphorane **31**, which, upon acyl transfer and hydrolysis, leads to the α-furanosyl amides **7**. An alternative pathway for **30** is represented by attack of O5 at the anomeric carbon, leading to the α-pyranosyl iminophosphorane **33**, acyl transfer from which would generate the α-galactopyranosyl amide **38**. This pathway does not appear to be followed, since no α-pyranosyl amide is observed in the ligation of furanosyl azides **5** and **13**. However, the reverse pathway, leading from **33** to **30**, is the source of α-furanosyl amide formation in the ligation of α-pyranosyl azide **39** and of the corresponding azide in the *gluco* series (**2**).[29,61] Acyl transfer in the α-pyranosyl iminophosphoranes **33** is relatively slow, allowing for ring-opening and phosphorus coordination by the 2-hydroxy group. The latter event prevents α–β isomerization of the pyranose ring to β-pyranosyl iminophosphorane **40**, and instead redirects the open sugar through the furanose pathway. Hence, attack of O4 on the anomeric carbon leads to **31** and thus to the α-furanosyl amide by-products in both the *galacto*- (**7**)[61] and *gluco*- (**4a**, Scheme 1) series.

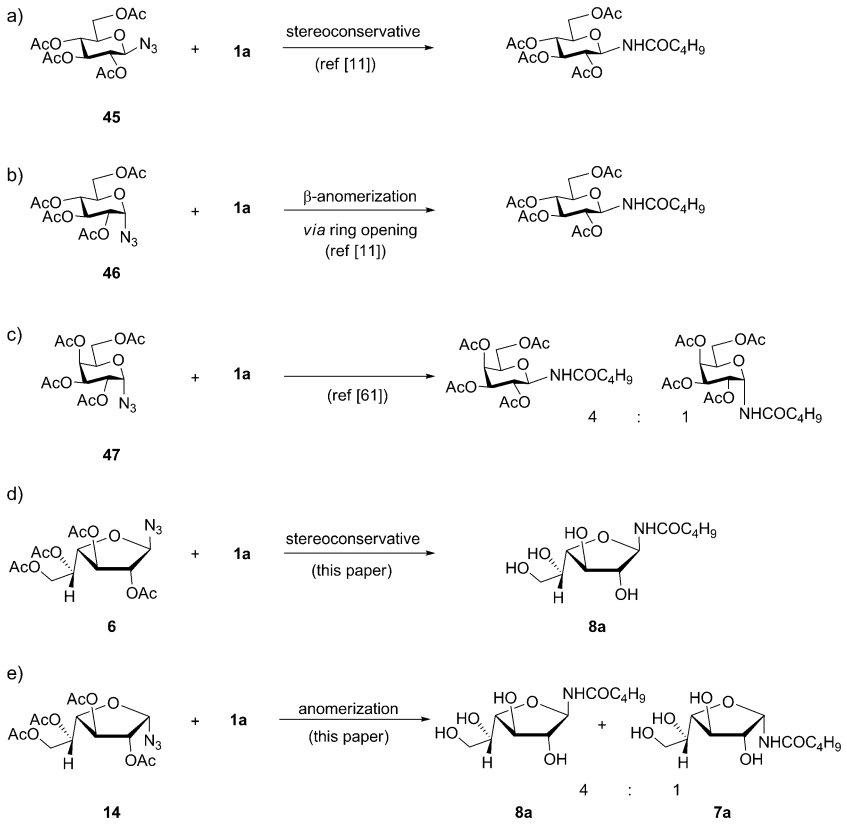
Thus, in this rather complex framework, the mechanism for the reaction of α-glucopyranosyl azide **2** with **1a**, as shown in Scheme 1, can be reformulated as proposed in Scheme 12. The α-iminophosphorane **43** formed by azide reduction can undergo either direct acyl transfer (to yield the α-pyranosyl amide **3a**) or ring-opening. This is probably not an equilibrium reaction, because the resulting phosphinimine is blocked by O–P coordination to afford **44**, which strongly favors the formation of [5.5]-fused bicyclic systems and hence ultimately affords **4a**. Indirect proof of this is provided by the absence of pyranosyl amides in the ligation products of furanosyl azides. Increasing the reaction temperature favors the ring-opening process, thus explaining the temperature dependence of the **3a**/**4a** ratio.[29a]

When the ligation is performed starting from an unprotected β-pyranosyl azide, a faster acyl transfer is expected. Thus, in the *gluco* series, a β-pyranosyl amide is the only reaction product (Scheme 1). However, if ring-opening of the β-pyranosyl iminophosphorane **40** (Scheme 11) can occur, the reaction can again be funneled through the cyclic oxazaphospholane **31**, thus providing a path for pyranose-to-α-furanose isomerization. This appears to be the case in some ligations of unprotected β-galactopyranosyl azide **42** (Scheme 11).[29b] Finally, the β-furanosyl iminophosphorane **28** (Scheme 11) must initially be formed upon reduction of β-galactofuranosyl azide **5**. This, however, appears to be incapable of direct acyl transfer but undergoes fast ring-opening leading, via **30** and **31**, to the α-furanosyl amide **7** (Scheme 11).

The results obtained concerning the ligation of pyranosyl and furanosyl tetra-*O*-acetyl-glycosyl azides with phosphine **1a** are summarized in Scheme 13. Ring-contraction or -expansion paths are not available to these fully *O*-acetylated substrates, so ring-opening events can only be detected as anomeric equilibration of the reaction products. Ligation of tetra-*O*-acetyl-β-glucopyranosyl azide **45** proceeds uneventfully to afford the β-glucopyranosyl amide (Scheme 13a). The same product is formed by ligation of the α-anomer **46** (Scheme 13b).[11] As previously discussed, complete inversion of the anomeric configuration observed in this reaction can be explained in terms of ring-opening of the intermediate iminophosphorane, facilitated by the electron-withdrawing effect of the acetyl groups, which favors phosphinimine formation. Similar behavior is observed for α-tetra-*O*-acetyl-galactopyranosyl azide **47** (Scheme 13c), although the anomeric inversion is not complete and a 4:1 β:α mixture of epimeric amides is formed.[61] This suggests that either acyl transfer is faster for the α-galactopyranosyl iminophosphorane than for the corresponding *gluco* derivative, or that the anomeric equilibrium in the galactopyranose series is less shifted toward the β-isomer. A similar 4:1 mixture of β- and α-furanosyl amides (**8a** and **7a**) was formed upon ligation of α-tetra-*O*-acetyl-galactofuranosyl azide **14** with **1a** (Scheme 13e). The partial inversion of anomeric configuration observed in this reaction suggests that when ring-opening occurs for galactofuranose, subsequent ring-clo-



Scheme 12. Furanosyl amide formation in the ligation of unprotected pyranosyl azides.



Scheme 13. Ligation of tetra-*O*-acetyl-glycosyl azides.

sure is biased towards the formation of 1,2-*trans*-amides, presumably for steric reasons. The same effect appears to allow a totally stereoconservative ligation of β-tetra-*O*-acetyl-galactofuranosyl azide **6** (Scheme 13d), which affords exclusively the corresponding β-tetra-*O*-acetyl-galactofuranosyl amide **8a**.

Conclusion

We have studied the traceless Staudinger ligation of glycofuranosyl azides with phosphines **1** and have discovered a stereoconvergent synthesis of glycofuranosyl amides that is independent of the configuration of the starting azide. Notably, both α- and β-isomers can be obtained with excellent selectivity from a common, easily available precursor. The steric course of the reaction is controlled by the C2 configuration of the sugar and by the protection state. Unprotected glycofuranosyl azides consistently afford amides of 1,2-*cis* configuration. The 1,2-*trans* counterpart is obtained starting from the corresponding *O*-acetyl-glycofuranosyl azides. For unprotected furanoses, the anomeric configuration appears to be dictated by O–P coordination, as supported by ^{31}P NMR studies. A convincing explanation for the formation of 1,2-*trans* products from *O*-acetyl-glycofuranosyl azides could not be achieved based on the empirical results collected here, but may now be addressed by future computational studies. From a synthetic point of view, however, it is worth noting that ligation with **1** is the only known process that allows the stereoselective reduction/acylation of furanosyl azides.[8g,49,62]

With these observations, we have now begun to clarify the complex mechanistic picture of the Staudinger ligation of glycosyl azides, both as pyranose and furanose isomers, to the point where predictions can be made concerning the stereochemistry of the reaction on new substrates and with new combinations of reagents. Work is in progress in our laboratory to test hypotheses generated by the models described above. The glycofuranosyl amides described in this work are novel glycoconjugates, of potential interest as bioactive compounds or new materials. Further studies are in progress to analyze the activity of galactofuranosyl amides against Gal*f*-containing pathogens.

Experimental Section

General: Solvents were dried by standard procedures: dichloromethane, methanol, *N*,*N*-diisopropylethylamine, and triethylamine were dried over calcium hydride; *N*,*N*-dimethylacetamide (DMA), 1,3-dimethyltetrahydro-2(1*H*)pyrimidinone (DMPU), chloroform, and pyridine were dried over activated molecular sieves. Reactions requiring anhydrous conditions were performed under nitrogen. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded at 400 MHz on a Bruker AVANCE-400 instrument. Chemical shifts (δ) in ^{1}H and ^{13}C spectra are expressed in ppm relative to Me_4Si as an internal standard. Chemical shifts (δ) in ^{31}P spectra are expressed in ppm relative to H_3PO_4 as an internal standard. Signals are abbreviated as s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Mass spectra were obtained with a Bruker Esquire 3000 ion-trap apparatus (ESI) and an FT-ICR mass spectrometer with APEX II & Xmass software (Bruker Daltonics) -4.7 Magnet. Optical rotations $[\alpha]_D$ were measured from solutions in a cell of pathlength 1 dm and capacity 1 mL with a Perkin–Elmer 241 polarimeter. Thin-layer chromatography (TLC) was carried out on pre-coated Merck F_{254} silica gel plates. Flash chromatography (FC) was carried out on columns of Macherey–Nagel silica gel 60 (230–400 mesh). The syntheses of phosphines **1a–g** and of β-*galacto*-furanosyl azides **5** and **6** have been described in the preliminary communication.[39] The syntheses and characterizations of *ribo*- and *arabino*-furanosyl azides **9**–**12** and of the corresponding pyranosyl isomers **18**–**21** are described in the Supplementary Information.

2,3,5,6-Tetra-*O*-*tert*-butyldimethylsilyl-α-D-galactofuranosyl azide (17): A solution of 1,2,3,5,6-penta-*O*-*tert*-butyldimethylsilyl-β-D-galactofuranose **15**[43] (200 mg, 0.26 mmol) in anhydrous CH_2Cl_2 (10 mL) was cooled to 0 °C and stirred for 10 min under nitrogen. Iodotrimethylsilane (1.2 equiv,

0.042 mL, 0.32 mmol) was then added, and the solution was stirred at 0 °C until TLC monitoring (hexane/AcOEt, 10:1) showed complete conversion of **15** into two products (R_f = 0.70 and R_f = 0.54). In parallel, a solution of tetrabutylammonium azide (0.5 M) was prepared.[63] A 10 M sodium hydroxide solution (280 μL) was added to tetrabutylammonium hydrogensulfate (383.3 mg, 1 mmol) in water (560 μL), then a solution of sodium azide (147 mg, 2.3 mmol) in water (280 μL) was added and tetrabutylammonium azide was extracted with dichloromethane (1 mL). The organic layer was separated and the aqueous phase was extracted with further dichloromethane (1 mL). The combined organic phases were dried with Na_2SO_4 and concentrated in vacuo at 40 °C to yield crude tetrabutylammonium azide as a white solid, which was redissolved in dry CH_2Cl_2 (2 mL). The solutions thus obtained were used directly in the following step.

Tetrabutylammonium azide solution (1 mmol) and EtN(*i*Pr)$_2$ (0.054 mL, 0.032 mmol) were added to the galactofuranosyl iodide, and stirring was continued until TLC revealed consumption of the components at R_f = 0.70 and R_f = 0.54. The solution was diluted with CH_2Cl_2, washed with 5% HCl, saturated aqueous $NaHCO_3$ solution, and water, dried (Na_2SO_4), and concentrated. The syrup obtained was purified by flash column chromatography (hexane/AcOEt, 98:2) to afford **17** in 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 5.11 (d, $J_{1,2}$ = 4 Hz, 1H; H-1), 4.24 (t, $J_{2,3}$ = 4.4, $J_{3,4}$ = 4.6 Hz, 1H; H-3), 3.99 (t, $J_{1,2}$ = 4, $J_{2,3}$ = 4.4 Hz, 1H; H-2), 3.87 (t, $J_{3,4}$ = 4.6, $J_{4,5}$ = 4.4 Hz, 1H; H-4), 3.79 (ddd, $J_{4,5}$ = 4.4, $J_{5,6}$ = 6, $J_{5,6'}$ = 5.6 Hz, 1H; H-5), 3.66 (dd, $J_{5,6}$ = 6, $J_{6,6'}$ = 10 Hz, 1H; H-6), 3.60 (dd, $J_{5,6'}$ = 5.6, $J_{6,6'}$ = 10 Hz, 1H; H-6′), 0.92–0.84 (m, 36H; SiC(CH$_3$)$_3$), 0.18–0.06 ppm (m, 24H; Si(CH$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 90.9 (C-1), 85.5 (C-4), 79.5 (C-2), 76.3 (C-3), 73.0 (C-5), 65.0 (C-6), 26.2, 26.1, 26.0, 25.9, −0.25 to −0.5 ppm; ESI-MS: *m*/*z* 684.4 [*M*+Na]$^+$.

α-D-Galactofuranosyl azide (13): A solution of **17** (60 mg, 0.09 mmol, 1 equiv) in anhydrous THF dry (180 μL) was cooled to 0 °C and stirred for 10 min under nitrogen. A 1 M solution of tetrabutylammonium fluoride in THF (450 μL, 0.45 mmol, 5 equiv) was added, and the mixture was stirred at room temperature until TLC monitoring (hexane/AcOEt, 60:40, and $CHCl_3$/MeOH, 80:20) showed complete transformation of **17** into **13**. The reaction mixture was diluted with water, washed with dichloromethane and AcOEt, and then concentrated. The syrup obtained was purified by flash column chromatography ($CHCl_3$/MeOH, 90:10). Quantitative yield. ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ = 5.17 (d, $J_{1,2}$ = 4.8 Hz, 1H; H-1), 4.08 (t, $J_{2,3}$ = 6.4, $J_{3,4}$ = 6 Hz, 1H; H-3), 4.04 (t, $J_{1,2}$ = 4.8, $J_{2,3}$ = 6.4 Hz, 1H; H-2), 3.77 (dd, $J_{3,4}$ = 6, $J_{4,5}$ = 4.4 Hz, 1H; H-4), 3.69 (ddd, $J_{4,5}$ = 4.4, $J_{5,6}$ = 5.2, $J_{5,6'}$ = 6.8 Hz, 1H; H-5), 3.66 (dd, $J_{5,6}$ = 5.2, $J_{6,6'}$ = 11.2 Hz, 1H; H-6), 3.60 ppm (dd, $J_{5,6'}$ = 6.8, $J_{6,6'}$ = 11.2 Hz, 1H; H-6′); ^{13}C NMR (100 MHz, CD_3OD, 25 °C): δ = 92.8 (C-1), 84.5 (C-4), 79 (C-2), 76.2 (C-3), 73.5 (C-5), 64.1 ppm (C-6); ESI-MS: *m*/*z*: 228.1 [*M*+Na]$^+$.

2,3,4,6-Tetra-*O*-acetyl-α-D-galactofuranosyl azide (14): Acetic anhydride (10 equiv) and a catalytic amount of *N*,*N*-dimethylaminopyridine were added to a 0.1 M solution of α-D-galactofuranosyl azide **13** (1 equiv) in pyridine at room temperature. The mixture was stirred for 24 h and then concentrated in vacuo. The residue was dissolved in AcOEt, and this solution was washed with aqueous 5% HCl, aqueous 5% $NaHCO_3$, and water. The organic layer was dried over Na_2SO_4 and concentrated to afford the product **14** in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 5.55 (d, $J_{1,2}$ = 5.6 Hz, 1H; H-1), 5.41 (t, $J_{2,3}$ = 6.8, $J_{3,4}$ = 6.4 Hz, 1H; H-3), 5.28 (ddd, $J_{4,5}$ = 2, $J_{5,6}$ = 4.8, $J_{5,6'}$ = 6.4 Hz, 1H; H-5), 5.14 (t, $J_{1,2}$ = 5.6, $J_{2,3}$ = 6.8 Hz, 1H; H-2), 4.35 (dd, $J_{5,6}$ = 4.8, $J_{6,6'}$ = 12 Hz, 1H; H-6), 4.17 (dd, $J_{5,6'}$ = 6.4, $J_{6,6'}$ = 12 Hz, 1H; H-6′), 4.13 (dd, $J_{3,4}$ = 6, $J_{4,5}$ = 4.4 Hz, 1H; H-4), 2.13 (s, 3H; OAc), 2.10 (s, 3H; OAc), 2.08 (s, 3H; OAc), 2.05 ppm (s, 3H; OAc); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 170.6, 170.2, 170.1, 169.9, 88.8 (C-1), 79.1 (C-4), 75.9 (C-2), 73.6 (C-3), 69.6 (C-5), 62.4 (C-6) 20.9–20.6 ppm (4×OAc); ESI-MS: *m*/*z*: 396.1 [*M*+Na]$^+$.

General procedure for the stereoselective ligation of glycosyl azides: Phosphine **1** (1.2 equiv) was added to a 0.1 M solution of glycosyl azide (1 equiv) in *N*,*N*-dimethylacetamide/DMPU (98:2) at room temperature. The mixture was stirred for 4 h at 70 °C, then water was added, and the resulting mixture was stirred for a further 2 h at the same temperature. The solvent was evaporated under reduced pressure, and the residue was purified as indicated below for each compound.

General procedure for the deprotection of per-*O*-acetyl-glycosyl amides

Procedure A: A 0.1 M solution of NaOMe in dry MeOH (0.5 equiv) was added, at room temperature and under nitrogen, to a 0.1 M solution of *O*-acetyl-glycosyl amide (1 equiv) in dry MeOH. The mixture was stirred at room temperature. After 45 min, TLC monitoring (hexane/AcOEt, 50:50, and $CHCl_3$/MeOH, 80:20) showed complete consumption of the starting material and Amberlyst IRA 120 H$^+$ was added. The mixture was stirred for 30 min at pH 3. The resin was then filtered off and washed with MeOH, and the solvent was removed under reduced pressure. The product, isolated in quantitative yield, was used without further purification.

Procedure B: The glycosyl amide (1 equiv) was dissolved in a 4 M solution of $MeNH_2$ in EtOH (0.046 M) and the mixture was stirred at room temperature. After 2 h, TLC monitoring (hexane/AcOEt, 50:50, and $CHCl_3$/MeOH, 90:10) showed complete consumption of the starting material. Evaporation of the solvent in vacuo and co-evaporation with MeOH afforded the unprotected amide without further purification.

***N*-Pentanoyl-α-D-ribofuranosyl amide (22a)**: This compound was obtained by ligation of **9** with **1a** and was purified by flash chromatography ($CHCl_3$/MeOH, 80:20). Yield: 59%. ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ = 5.67 (d, $J_{1,2}$ = 4.8 Hz, 1H; H-1), 4.12–4.06 (m, 2H; H-2, H-3), 3.93–3.87 (q, $J_{4,5}$ = 3.2 Hz, $J_{4,5'}$ = 4.4 Hz, 1H; H-4), 3.69 (dd, $J_{4,5}$ = 3.2 Hz, $J_{5,5'}$ = 12 Hz, 1H; H-5), 3.55 (dd, $J_{4,5'}$ = 4.4 Hz, $J_{5,5'}$ = 12 Hz, 1H; H-5′), 2.24 (t, J = 7.2 Hz, 2H; CH$_2$), 1.65–1.57 (m, 2H; CH$_2$), 1.43–1.33 (m, 2H; CH$_2$), 0.95 ppm (t, J = 7.2 Hz, 3H; CH$_3$); ^{13}C NMR (100 MHz, CD_3OD, 25 °C): δ = 176.6, 84.2 (C-4), 81.5 (C-1), 72.6, 71.8, 62.9 (C-5), 36.9 (CH$_2$), 28.8 (CH$_2$), 23.3 (CH$_2$), 14.1 ppm (CH$_3$); FT-ICR (ESI): calcd for $C_{10}H_{19}NO_5$ [*M*+Na]$^+$ 256.12632; found 256.12643.

2,3,5-Triacetyl-*N*-pentanoyl-α-D-ribofuranosyl amide (59): Ac_2O (10 equiv) and a catalytic amount of *N*,*N*-dimethylaminopyridine were added to a 0.1 M solution of substrate **22a** (1 equiv) in dry pyridine at room temperature. The mixture was stirred for 24 h and then concentrated in vacuo. The residue was dissolved in AcOEt, and this solution was washed with aqueous 5% HCl, aqueous 5% $NaHCO_3$, and water. The organic layer was dried over Na_2SO_4 and concentrated to give the product in quantitative yield. ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ = 6.06 (d, $J_{1,2}$ = 4.8 Hz, 1H; H-1), 5.45 (t, $J_{1,2}$ = 4.8, $J_{2,3}$ = 5.6 Hz, 1H; H-2), 5.36 (t, $J_{2,3}$ = 5.6 Hz, 1H; H-3), 4.36–4.31 (m, 2H; H-4, H-5), 4.21 (dd, $J_{4,5'}$ = 4.8, $J_{5,5'}$ = 12 Hz, 1H; H-5′), 2.23 (t, J = 7.2 Hz, 2H; CH$_2$), 2.19 (s, 3H; OAc), 2.15 (s, 3H; OAc), 2.12 (s, 3H; OAc), 1.67–1.59 (m, 2H; CH$_2$), 1.44–1.35 (m, 2H; CH$_2$), 0.99 ppm (t, J = 7.2 Hz, 3H; CH$_3$); ^{13}C NMR (100 MHz, CD_3OD, 25 °C): δ = 176.1, 172.2, 171.5, 171.3, 80.8 (C-1), 79.2 (C-4), 72.9 (C-3), 71.9 (C-2), 64.8 (C-5), 36.8 (CH$_2$), 29 (CH$_2$), 23.4 (CH$_2$), 20.7–20.5 (3×OAc), 14.2 ppm (CH$_3$); ESI-MS: *m*/*z*: 359.1 [*M*+Na]$^+$.

***N*-Pentanoyl-β-D-ribofuranosyl amide (23a)**: Reaction of **10** with **1a** afforded tri-*O*-acetyl-*N*-pentanoyl-β-D-ribofuranosyl amide. After deacetylation (procedure B), the compound was purified by flash chromatography ($CHCl_3$/MeOH, 80:20). Yield: 55%. ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ = 5.38 (d, $J_{1,2}$ = 4.8 Hz, 1H; H-1), 4.06 (t, $J_{2,3}$ = 5.2, $J_{3,4}$ = 5.2 Hz, 1H; H-3), 3.91 (t, $J_{1,2}$ = 4.8, $J_{2,3}$ = 5.2 Hz, 1H; H-2), 3.88–3.83 (q, $J_{4,5}$ = 3.6 Hz, $J_{4,5'}$ = 4.4 Hz, 1H; H-4), 3.70 (dd, $J_{4,5}$ = 3.6 Hz, $J_{5,5'}$ = 12 Hz, 1H; H-5), 3.61 (dd, $J_{4,5'}$ = 4.4 Hz, $J_{5,5'}$ = 12 Hz, 1H; H-5′), 2.23 (t, J = 7.2 Hz, 2H; CH$_2$), 1.65–1.57 (m, 2H; CH$_2$), 1.43–1.33 (m, 2H; CH$_2$), 0.95 ppm (t, J = 7.2 Hz, 3H, CH$_3$); ^{13}C NMR (100 MHz, CD_3OD, 25 °C): δ = 176.8, 85.8 (C-1), 85.1 (C-4), 75.9 (C-2), 71.9 (C-3), 63.3 (C-5), 37.1 (CH$_2$), 28.9 (CH$_2$), 23.5 (CH$_2$), 14.3 ppm (CH$_3$); FT-ICR (ESI): calcd for $C_{10}H_{19}NO_5$ [*M*+Na]$^+$ 256.12632; found 256.12627.

***N*-Pentanoyl-β-D-arabinofuranosyl amide (24a)**: The compound was obtained by ligation of **11** with **1a** and was purified by flash chromatography ($CHCl_3$/MeOH, 80:20). Yield: 57%. ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ = 5.72 (d, $J_{1,2}$ = 4.4 Hz, 1H; H-1), 4.01 (t, $J_{2,3}$ = 3.6 Hz, $J_{3,4}$ = 3.6 Hz, 1H; H-3), 3.90 (dd, $J_{1,2}$ = 4.4 Hz, $J_{2,3}$ = 3.6 Hz, 1H; H-2), 3.76 (ddd, $J_{3,4}$ = 3.6 Hz, $J_{4,5}$ = 3.6 Hz, $J_{4,5'}$ = 5.2 Hz, 1H; H-4), 3.70 (dd, $J_{4,5}$ = 3.6 Hz, $J_{5,5'}$ = 11.6 Hz, 1H; H-5), 3.64 (dd, $J_{4,5'}$ = 5.2 Hz, $J_{5,5'}$ = 11.6 Hz, 1H; H-5′), 2.28 (t, J = 7.6 Hz, 2H; CH$_2$), 1.65–1.57 (m, 2H; CH$_2$), 1.43–1.33 (m, 2H; CH$_2$), 0.94 ppm (t, J = 7.6 Hz, 3H; CH$_3$); ^{13}C NMR (100 MHz, CD_3OD, 25 °C): δ = 176.8, 84.4 (C-4), 82.2 (C-1), 78.3 (C-3), 77.3 (C-2),

63.5 (C-5), 36.9 (CH_2), 28.9 (CH_2), 23.5 (CH_2), 14.3 ppm (CH_3); FT-ICR (ESI): calcd for $C_{10}H_{19}NO_5$ $[M+Na]^+$ 256.12632; found 256.12605.

***N*-Pentanoyl-α-D-arabinofuranosyl amide (25a)**: Reaction of **12** with **1a** afforded tri-*O*-acetyl-*N*-pentanoyl-α-D-arabinofuranosyl amide. After deacetylation (procedure B), the compound was purified by flash chromatography ($CHCl_3$/MeOH, 80:20). Yield: 53%. ^{1}H NMR (400 MHz, CD_3OD, 25°C): $\delta = 5.39$ (d, $J_{1,2} = 4.8$ Hz, 1H; H-1), 4.03 (t, $J_{2,3} = 5.2$ Hz, 1H; H-3), 3.88 (t, $J_{1,2} = 4.8$, $J_{2,3} = 5.2$ Hz, 1H; H-2), 3.84 (q, $J_{4,5} = 3.6$ Hz, $J_{4,5'} = 4.4$ Hz, 1H; H-4), 3.67 (dd, $J_{4,5} = 3.6$, $J_{5,5'} = 12$ Hz, 1H; H-5), 3.55 (dd, $J_{4,5'} = 4.4$ Hz, $J_{5,5'} = 12$ Hz, 1H; H-5′) 2.20 (t, $J = 7.6$ Hz, 2H; CH_2), 1.60–1.54 (m, 2H; CH_2), 1.40–1.29 (m, 2H; CH_2), 0.92 ppm (t, $J = 7.2$ Hz, 3H; CH_3); ^{13}C NMR (100 MHz, CD_3OD, 25°C): $\delta = 177.1$, 85.7 (C-1), 85 (C-4), 81.5 (C-3), 77.1 (C-2), 63.1 (C-5), 37.1 (CH_2), 28.9 (CH_2), 23.5 (CH_2), 14.3 ppm (CH_3); FT-ICR (ESI): calcd for $C_{10}H_{19}NO_5$ $[M+Na]^+$ 256.12632; found 256.12638.

***N*-Pentanoyl-β-D-ribopyranosyl amide (26a)**: a) The compound was obtained by ligation of **18** with **1a** and was purified by flash chromatography ($CHCl_3$/MeOH, 80:20). Yield: 68%. b) Reaction of **19** with **1a** afforded tri-*O*-acetyl-*N*-pentanoyl-α-D-ribopyranosyl amide. After deacetylation (procedure A), the compound was purified by flash chromatography ($CHCl_3$/MeOH, 80:20). Yield: 55%. ^{1}H NMR (400 MHz, CD_3OD, 25°C): $\delta = 5.15$ (d, $J_{1,2} = 9.2$ Hz, 1H; H-1), 4.07 (d, $J_{2,3} = 2.8$ Hz, 1H; H-3), 3.73–3.57 (m, 3H; H-4, H-5, H-5′), 3.39 (dd, $J_{1,2} = 9.2$, $J_{2,3} = 2.8$ Hz, 1H; H-2), 2.22 (t, $J = 7.6$ Hz, 2H; CH_2), 1.64–1.56 (m, 2H; CH_2), 1.43–1.32 (m, 2H; CH_2), 0.94 ppm (t, $J = 7.6$ Hz, 3H; CH_3); ^{13}C NMR (100 MHz, CD_3OD, 25°C): $\delta = 177.5$, 78.0 (C-1), 72.4 (C-3), 71.3 (C-2), 68.8 (C-4), 65.7 (C-5), 37.0 (CH_2), 28.9 (CH_2), 23.5 (CH_2), 14.3 ppm (CH_3); FT-ICR (ESI): calcd for $C_{10}H_{19}NO_5$ $[M+Na]^+$ 256.12632; found 256.12645.

***N*-Pentanoyl-β-L-arabinopyranosyl amide (27a)**: a) The compound was obtained by ligation of **20** with **1a** and was purified by flash chromatography ($CHCl_3$/MeOH, 80:20). Yield: 70%. b) Reaction of **21** with **1a** afforded tri-*O*-acetyl-*N*-pentanoyl-α-D-arabinopyranosyl amide. After deacetylation (procedure A), the compound was purified by flash chromatography ($CHCl_3$/MeOH, 80:20). Yield: 57%. ^{1}H NMR (400 MHz, CD_3OD, 25°C): $\delta = 4.90$ (d, $J_{1,2} = 8$ Hz, 1H; H-1), 3.95–3.88 (m, 2H; H-3, H-5), 3.73–3.66 (m, 3H; H-2, H-4, H-5′), 2.34 (t, $J = 7.6$ Hz, 2H; CH_2), 1.74–1.67 (m, 2H; CH_2), 1.53–1.42 (m, 2H; CH_2), 1.03 ppm (t, $J = 7.6$ Hz, 3H; CH_3); ^{13}C NMR (100 MHz, CD_3OD, 25°C): $\delta = 177.2$, 81.8 (C-1), 75.3 (C-2), 71.4 (C-4), 70.3 (C-3), 68.9 (C-5), 37.1 (CH_2), 29.0 (CH_2), 23.5 (CH_2), 14.2 ppm (CH_3); FT-ICR (ESI): calcd for $C_{10}H_{19}NO_5$ $[M+Na]^+$ 256.12632; found 256.12621.

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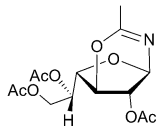

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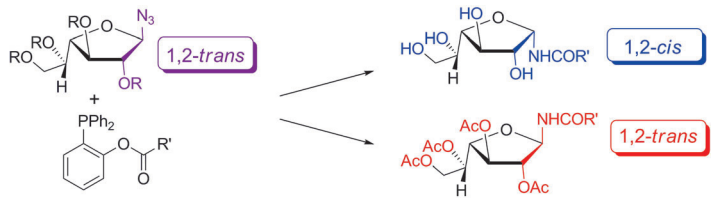

Without a trace: A highly stereoselective synthesis of both α- and β-glycofuranosyl amides based on the traceless Staudinger ligation of glycofuranosyl azides of the *galacto*, *ribo*, and *arabino* series with 2-diphenylphosphanylphenyl esters is reported (see scheme). The process does not depend on the anomeric configuration of the starting azide but appears to be controlled by the C2 configuration and by the protection/deprotection state of the substrates.

Carbohydrates

*F. Nisic, G. Speciale, A. Bernardi** ..... ▮▮▮▮–▮▮▮▮

Stereoselective Synthesis of α- and β-Glycofuranosyl Amides by Traceless Ligation of Glycofuranosyl Azides