A Highly Efficient Approach to the Synthesis of Complex α-Glycosyl Phosphosaccharides

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Abstract: A highly efficient and stereoselective approach to the synthesis of biologically important and complex α-glycosyl phosphosaccharides (GPSs) has been disclosed, employing direct gold(I)-catalyzed glycosylation of the weakly nucleophilic phosphoric acid acceptors. The broad substrate scope is demonstrated with more than 45 examples, including glucose (Glc), xylose, glucuronatose, galactose (Gal), mannose (Man), rhamnose (Rha), fucose (Fuc), 2-N$_3$-2-dexoxymannose (ManN$_3$), 2-N$_3$-2-dexoxyglucose (GlcN$_3$), 2-N$_3$-2-dexoxygalactose (GalN$_3$) and unnatural carbohydrates. Moreover, the glycosyl phosphotriester prepared herein was successfully applied to the one-pot synthesis of a GPS from *Leishmania donovani*, and an effective preparation of a trisaccharide diphosphate of GPS fragments from *Hansenula capsulate* via iterative elongation strategy is realized.

Introduction

GPSs represent a large and important family of complex glycans, which are ubiquitously distributed in bacteria, yeasts, protozoan parasites, and animals, and exhibit numerous bio-functions including bacterial infections, cell adhesive, immunoresponse, and antimicrobial (Figure 1B)\(^1\)\(^-\)\(^5\). The GPSs consist of anomeric glycosyl phosphates in which the anomeric position of one constituent glycan was linked to another one mainly by α-type phosphodiester linkage (Figure 1A). In the process of carbohydrate metabolism, the constituent glycosyl phosphates (GPs) are significant intermediates\(^6\). Syntheticly, protected GPs have been utilized as effective glycosyl donor reagents\(^7\), and under the catalysis of bis-thiourea, the armed GPSs proceed an S$_\text{N}$-2 glycosylation pathway\(^8\). Despite the significance of GPSs, efficient approaches to access GPSs are rather limited: isolation from cell culture hardly affords homogeneous sample and chemical synthesis remains challenging due to the character of complex structure. Accordingly, efficient methods of constructing homogeneous GPSs and GPs are still in great demand.
In addition to intrinsically labile character, the anomeric stereocontrol of forming α-GPSs, most of which assume 1,2-cis configuration, is regarded as a challenging task. The synthetic method of H-phosphonate chemistry has found extensive applications in the synthesis of α-GPSs, while two-step transformations of nucleophilic displacement and oxidation are inevitable (Scheme 1A). Nevertheless, the resulted phosphate anions render product incompatible with follow-up or late-stage chemical modifications to increase molecular complexity and diversity. The alternative approach employing phosphoramidite displays great success in installation of phosphoester, yet is rarely applied to synthesis of anomeric GPS probably due to issues of diastereo-selectivity and undesired oxidative cleavage reaction (Scheme 1B).
Scheme 1. Profile of approaches to glycosyl phosphosaccharides

A) The H-phosphonate method:

\[
\begin{align*}
\text{Promoter} & \quad \text{one step} \\
\text{R} = \text{OC(NH)CCl}_3, \text{SPh, OH, 3-methoxypyridin-2-yl, 4-pentenyloxy etc.}
\end{align*}
\]

B) The phosphoramidite method:

\[
\begin{align*}
\text{Promoter} & \quad \text{one step} \\
\text{R} = \text{OC(NH)CCl}_3, \text{SPh, OH, 3-methoxypyridin-2-yl, 4-pentenyloxy etc.}
\end{align*}
\]

C) The glycosylation methods:

\[
\begin{align*}
\text{Promoter} & \quad \text{one step} \\
\text{R} = \text{OC(NH)CCl}_3, \text{SPh, OH, 3-methoxypyridin-2-yl, 4-pentenyloxy etc.}
\end{align*}
\]

D) This work:

\[
\begin{align*}
\text{Promoter} & \quad \text{one step} \\
\text{R} = \text{OC(NH)CCl}_3, \text{SPh, OH, 3-methoxypyridin-2-yl, 4-pentenyloxy etc.}
\end{align*}
\]

One-step and direct glycosylation of phosphate acceptors with glycosyl donors represents a convergent and concise method for the synthesis of α-GPSs, which does not require oxidation transformation (Scheme 1C). This glycosylation strategy to access α-GPSs was previous realized by utilizing glycosyl trichloroacetimidate as donor and the weak nucleophile of phosphoric acid as acceptor under the action of strong acid\textsuperscript{24}, and later, by a panel of donors with different leaving groups (e.g. SPh, 3-methoxypyridin-2-yl, pentenyloxy)\textsuperscript{25-31}. The efficiency of these glycosylation reactions with phosphates as acceptors remains unmet: 1) the yield was deteriorated when strong acid was used to realize α-stereoselectivity\textsuperscript{24}, 2) stoichiometric base was applied to preserve the entity of GPs, but leading to poor 1,2-\textit{cis} stereoselectivity\textsuperscript{28}, 3) only a handful of complex disaccharide GPSs were accessed by using the direct glycosylation strategy with phosphate anion as acceptor\textsuperscript{25}.

Catalytic glycosylation methods have emerged as an appealing approach to the synthesis of carbohydrates, which feature less promoter and waste, and high efficiency\textsuperscript{32}. Among those, alkynylphilic gold(I) catalysis has been extensively applied in the syntheses of numerous complex glycans and glycoconjugates\textsuperscript{33}, along with other natural products\textsuperscript{34}, by exploiting the compatibility with oxygen-containing functionalities\textsuperscript{35}. Especially, glycosyl donor with \textit{ortho}-alkynylbenzoate as leaving group first introduced by Yu and coworkers can glycosylate a variety of acceptors\textsuperscript{36,37}. Nevertheless,
the glycosylation of exceedingly poor nucleophile of phosphoric acid remains elusive, which entails mild conditions free from competitive nucleophilic species. We herein disclose a stereoselective and general approach to the synthesis of α-GPs and α-GPSs via a gold(I)-catalyzed glycosylation method with glycosyl ortho-alkynylbenzoate as donor and weakly nucleophilic phosphoric acid as acceptor. While the alkynylphilicity of gold(I) catalysis has been widely investigated and applied, the Lewis acid property when oxygen-containing functionalities is activated by gold(I) remains much less explored. Herein, both the alkynylphilicity and weak acidity of gold(I) catalyst are capitalized on to initiate the glycosylation reaction and promote epimerization to α-anomer, respectively (Scheme 1D). Moreover, the anomeric effect of phosphoric acid in the glycosylation reaction is also exploited to direct the α-selectivity under the present weakly acidic condition.38,39

**Results and Discussions**

To test the validity of this proposal, tetrabenzy1 glucoside 1a was examined with a structurally simple acceptor of phosphoric acid dibenzyl ester 2a (Table 1). Initial experiment gave promising results with good yield (88%) and α-selectivity (α/β = 2.8/1, entry 1). Thus, detailed optimizations were subsequently conducted by tuning reaction temperature, solvent and additives. As depicted in Table 1, lowering temperature was not effective (83%, α/β = 2/1, entry 2); varying the anion in the catalysis with OTf diminished α-selectivity (entry 3); switching to solvent of ether and additive of Ph3P=O did not provide satisfactory results though they were effective in the case of alcohol acceptor (entry 4-6). Gratifyingly, the diastereoselective ratio was raised to 10/1 by an added HO Tf (0.1 equiv.), which is supposed to thermodynamically equilibrated β-anomer to the α-one, but compromise the overall yield (62%, entry 7). In contrast, heterogenous acidic H+ resin did not affect the diastereoselectivity (entry 8). Hence, the homogeneous Lewis acid of gold(I) catalysis was anticipated to activate the armed glycosyl phosphate under an elevated temperature. Indeed, after complete glycosylation of 2a at 0 °C for 0.5 h, keeping the mixture at 60 °C for 2 h in non-coordinating CICH2CH2Cl (DCE) for anomerization produced the α-anomer in good selectivity (α/β = 9/1) without deteriorating yield (87%, entry 9). Further elevation of temperature (75 °C and 95 °C) resulted in a drop of yield or decomposition of product (entry 10, 11). Fortunately, increasing the equivalence of donor 1a to 1.5 relative to acceptor 2a (1.0 equiv.) reached an exceptional ratio of 16/1 in an excellent yield of 93% (entry 12).
Next, we wondered whether this gold (I)-catalyzed glycosylation strategy was amenable to various glycosyl donors outfitted with different protecting groups or configurations (Table 2). First, donor 1b, of which the BnOCH$_2$ moiety is omitted compared to 1a, delivered the expected xylosyl phosphate 3b in good yield and diastereoselectivity (78%, 11/1) by utilizing the aforementioned protocol. Replacing BnOCH$_2$ moiety with electron-withdrawing groups such as AcOCH$_2$ and COOMe may greatly reduce the reactivity of donor, thereby causing difficulty in epimerization. Luckily, the 6-OAc product (3c) could be reached in a diastereoselective ratio of 12/1 merely at room temperature, of which α-selectivity is presumably dominated by anomeric effect. For the other one equipped with COOMe, the product (3d) can be epimerized to enrich α-anomer (9.7/1) under higher temperature of 100 °C with a good yield of 87%.

Consequently, this strategy was extended to a variety of donors including Gal, Man, ManN$_3$, Rha, Fuc, GlcN$_3$, GalN$_3$ and unnatural carbohydrates (Table 2). For the production of those with highly anomeric effect and dominated by steric hindrance, such as galactosyl phosphate (3e and 3e'), mannosyl phosphate (3f and 3f'), disarmed 2-N$_3$-2-dexoy-mannosyl phosphate (3g), rhamnosyl...
phosphate (3h) and fucosyl phosphate (3i), an operationally simple procedure at room temperature was effective to access desired products in highly diastereoselective manners and excellent yields. However, switching to phenyl tetrabenzyl-1-thio-mannoside which was preactivated with p-TolSCl and AgOTf, followed by addition of 2a, gave only byproduct 3p derived from intramolecular cyclization\(^\text{40}\). Among those, 3g represents constituent unit derived from capsule polysaccharide of Neisseria meningitidis\(^\text{A}\)\(^\text{41}\). The straightforward syntheses of extremely unstable diphenyl phosphate 3e\(^\star\) and 3f\(^\star\) demonstrate the utility of this strategy for directly glycosylating weakly nucleophilic phosphoric acid. Moreover, 3f can be obtained on a 1.2 g scale with low catalytic loading of Ph\(_3\)PAuNTf\(_2\) (0.5 mol%) albeit in slightly decreased diastereoselectivity (17/1) and yield (87%)\(^\text{42}\). The deprotected form of 3f might serve as replacement therapy for the disease of congenital disorder of glycosylation type Ia, which is under clinical trial\(^\text{43}\). Interestingly, 1,2-cis α-fucosyl phosphate 3i was obtained even with neighboring-participating Bz situated at 2-O, demonstrating the strong anomeric effect in the case of phosphoric acid as acceptor. However, the diastereoselectivity can be reversed by adding extra base of iPr\(_2\)NEt (0.2 equiv.) to form phosphate anion as acceptor.

Because of the distinct nature of N\(_3\) substituent in comparison with OBn, formation of 1,2-cis α-D-glycosamine glycosidic bond remains elusive in the case of alcohols as acceptors\(^\text{14-17}\). Although the azido substituted glycosyl phosphates are resistant to epimerization at high temperature, donors of tribenzyl GlcN\(_3\) and GalN\(_3\) underwent smoothly coupling reactions with useful diastereoselective ratios of 8.6/1 (3j) and 7.3/1 (3k) which might find utility in the synthesis of Lipid A or other phosphosaccharides\(^\text{2,44}\).

Derivatization and mimicking of natural glycosyl phosphates emerge as attractive tools to elucidate molecular mechanism of glycosyltransferases and discover novel therapeutic reagents\(^\text{45,46}\)\(^\star\). Herein, a panel of fluorine-substituted α-GPs (3l-3o) were readily assembled via gold(I)-catalyzed glycosylation approach. Notably, the highly α-selective outcomes are in stark contrast to the reported results of fluorine-directed glycosylation with alcohol acceptors\(^\text{47}\).
Table 2. The Reaction Scope of Various Glycosyl Donors

| Glycosyl Donor | Product | Yield (%) | Ratio (α:β) |
|----------------|---------|-----------|-------------|
| 2a (R¹ = Bn)  | 3b      | 78%       | 11/1        |
| 2a' (R¹ = Ph) | 3c      | 88%       | 12/1        |
| 3b-3o (yield, α/β) | R¹ = Bn or Ph | 69% - 94% | 7.7/1 - 13/1 |

After determining the generality of various glycosyl donors which glycosylated with phosphoric acid 2a, we explored the possibility of extension to more complex phosphate nucleophiles. Thus, a set of structurally diverse acceptors of phosphoric acid glycosyl/peptidyl esters were readily prepared.
through a straightforward route of phosphorylation of alcohol and subsequent debenzylolation (see SI), including 6-O-benzylxyophosphoryl glucoside 2b and 2c, sterically hindered 4-O-benzylxyophosphoryl glucoside 2d and galactoside 2e, and 3-O-benzylxyophosphoryl glucoside 2f outfitted with labile groups of TBS and benzylidene (Table 3). The carbohydrates widely distributed in natural GPSs were selected as glycosyl donors (Glc (1a), Gal (1e), Man (1f), Rha (1h), GlcN (1j), GalN (1k)), which led to twenty-seven bis-glycosyl benzylphosphotriesters. For convenience of characterization, the phosphorus chirality was eliminated by hydrogenolysis of benzyl phosphates (4a-4za), which simultaneously resulted in reduction of N (4t-4z, 4za, 4e, 4j, 4o). In detail, by using the protocol of glycosylation and subsequent anomerization, condensation of Glc donor (1a) and all the five acceptors (2b-2f) delivered the corresponding GPSs (4a-4e) in highly diastereoselective manners and yields. The donors of Gal (1e), Man (1f) and Rha (1h) with highly anomeric effect produced GPSs (4f-4s) in invariably high α-selectivities and excellent yields. Although azide substituted substrates of GlcN (3) and GalN (3) are resistant to epimerization and display weaker α-configured bias, good results were attained with consistent stereoselectivities and quantitative yields (4t-4v, 4x-4z, 4za), except 4w which was formed in low stereoselectivity (3/1).
Furthermore, one of phosphoglycopeptides (4zb), which are found in parasites, was concisely assembled via glycosylation of threonyl phosphate 2g in a stereospecific manner, albeit in a low yield of 60% because of limited solubility of 2g in DCE\textsuperscript{68} (Scheme 2).
While one-pot glycosylation protocol emerges as versatile strategy to synthesize complex oligo/polysaccharides of which the units are tethered by acetal linkages, this strategy is not applicable to the assembly of conventionally synthesized bis-glycosyl phosphodiester which incorporate reactive functionality of phosphate anion. Gratifyingly, bis-glycosyl benzyl phosphotriesters readily prepared in our system could serve as attractive substrates for one-pot glycosylation, and described in Scheme 3 is an example, in which linker-tethered was assembled in one pot via gold(I)-catalyzed glycosylation reaction and a follow-up orthogonal coupling promoted by NIS and TMSOTf. The chirality of phosphorus atom can be eliminated by converting OBn to O-, generating a single stereomer (6) derived from phosphosaccharide of *Leishmania donovani*.1

**Scheme 3. One-pot Synthesis of GPS 6**

Finally, the utility of this gold(I)-catalyzed one-step approach to synthesis of GPSs was further illustrated by iterative elongation of phosphomannosyl fragments from *Hansenula capsulate* (Scheme 4). First, condensation of donor 1q and acceptor 2i furnished the desired phosphotriester 4zc. Because 4zc was resistant to preactivation by using p-TolSCl/AgOTf or BSP/Tf₂O which led to only 30% yield and armed donor with benzyl groups was prone to give cyclized byproduct (e.g. 3p), SPh was converted to *ortho*-alkynylbenzoate as leaving group via two steps. Next, condensation of 7 and 2i
generated a trisaccharide 8 consisting of two phosphotriester functionalities in good yield (70%), which was subsequently converted to trisaccharide donor 9 in a procedure similar to that for 7. As a late-stage chemical modification on this trisaccharide, a third glycosylation reaction between donor 9 and 3-azidopropanol was performed to install a linker with the two present phosphotriesters intacted. Finally, the resulting trisaccharide was globally deprotected under mild conditions to afford an amino-linker tethered trisaccharide diphosphate 10.

Scheme 4. The synthetic route to GPS 10 via late-stage modification

Conclusion

In conclusion, we have developed a highly efficient and stereoselective approach to the synthesis of GPSs by employing gold(I)-catalyzed glycosylation of phosphoric acid acceptors. The efficiency of this protocol was demonstrated by its universal application in preparing more than 45 complex GPSs, one-pot synthesis of linker-tethered GPS from *Leishmania donovani*, and an effective preparation of trisaccharide diphosphate from *Hansenula capsulate* via iterative elongation. Because of its exceptionally broad substrate scope, high α-selectivity and inertness of phosphotriester toward chemical manipulations in comparison to phosphodiester, this strategy will offer new opportunities to create complex polyphosphosaccharides and incorporate diverse phosphosaccharides into bioactive molecules.
Keywords: phosphosaccharide • glycosyl phosphate • stereoselectivity • glycosylation • gold(I) catalysis

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