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COMMUNICATION

Propargyl/methyl furanosides as potential glycosyl donors†‡

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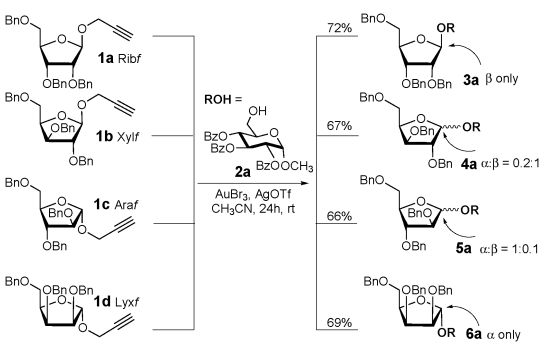
Transfuranosylations are not well studied though many similar studies exist for transpyranosylation; herein, we report that propargyl/methyl D-rib*f*- and D-lyx*f*- give only 1,2-*trans* glycosides whereas D-ara*f*- and D-xyl*f*- result in a mixture of 1,2-*trans* and 1,2-*cis* glycosides; observed facts are rationalised by computational studies.

Complex carbohydrate components of glycoproteins and glycolipids are undoubtedly shown to be powerful in a variety of biochemical and physiological processes in animals, yeast, cell-cell adhesion, cytolysis, fertilization and hormone action.[1] Synthesis of complex oligosaccharides is still a formidable task in spite of several elegant approaches and as a consequence superior methods for glycosidation need to be discovered.[2] Ironically, most of the pioneering efforts are dedicated to methods for the synthesis of pyranosides either because of their more frequent occurrence in nature than furanosides or due to the complexity in synthesizing them.[3] However, recent identification of oligofuranosides in many natural products alerted synthetic chemists to develop novel furanosylation methods which are mild, stereoselective and catalytic from easily available starting monosaccharides.[4] Glycosyl phosphatidyl inositol,[5a,b] arabinogalactan (AG),[5c] lipoarabinomannan (LAM)[5c] and helminothosporium toxins[5d] are some of the examples that contain complex oligofuranosides with immense biological importance.[5]

From our laboratory, we identified propargyl and methyl glycopyranosides as glycosyl donors by the use of gold(III) halides.[6a,b] The methodology is unique as it requires only a catalytic amount of gold(III) salts and is traceless (no side product from the leaving group) with a large substrate scope.[6]

The ability of methyl glycosides to behave as glycosyl donors was linked to the Lewis and Brønsted acidity of $AuBr_3$ in the presence of aglycons. In addition, recently, the gold(III) activation protocol has been found to be excellent for the synthesis of transglycosylated products from 2-*C* nitromethyl-containing methyl glycosides,[7a] glyco-amino acid building blocks,[7b] glycopolymers[7c] and glycopolypeptides.[7d] The foregoing discussion enticed us to probe the gold activation procedure for furanosylations with an eventual goal to synthesize antigenic motifs of LAM and AG present in *Mycobacterium tuberculosis*.[5b] Accordingly, D-rib*f* (**1a**), D-xyl*f* (**1b**), D-ara*f* (**1c**) and D-lyx*f* (**1d**) were synthesized from the corresponding aldoses by simple Fischer glycosidation[8] as the key step followed by per-*O*-benzylation. Initially, propargyl ribofuranoside **1a** was allowed to react with aglycon **2a** in the presence of $AuBr_3$ in CH_3CN at room temperature for more than 3 days to observe formation of the transglycosylated disaccharide **3a** in 40% yield in 1,2-*trans* (β-) fashion only (Scheme 1). The overall yield could be improved to 72% without compromising on the 1,2-*trans* stereoselectivity by the addition of 8 mol% each of $AuBr_3$ and AgOTf.[9] Encouraged by the observed 1,2-*trans* stereoselectivity, xyl*f* **1b** was subjected to same reaction conditions with aglycon **2a** to observe the 5 : 1 diastereomeric mixture of the 1,2-*trans* (β-) and 1,2-*cis* (α-) disaccharides **4a** in 67% yield. Similar experiments with ara*f* derivative **1c** gave again diastereomeric mixture of 10 : 1 1,2-*trans* (α-) and 1,2-*cis* (β-) disaccharides **5a** in 66% yield whereas D-lyx*f* derivative **1d** resulted in 1,2-*trans* (α-) isomer **6a** only in 69% yield (Scheme 1).[9]

To better understand the reasons for the observed experimental trends, molecular modelling calculations have been performed. Initially conformational searches for the reactants, in their ionic forms, and products were carried-out by employing the OPLS_2005 force field, using the ConfGen module of the Schrödinger program package.[10] This was followed by quantum chemical calculations on all the conformations generated, with



Scheme 1 Propargyl furanosides as glycosyl donors.

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‡ Electronic supplementary information (ESI) available. See DOI: 10.1039/c1cc13134f

Table 1 Furanosides as glycosyl donors

Glycosyl donor	R_5OH	Product	Time, %Yield α : β ratio
rib*f*-Series			
1a	**2b**	**3b**	12 h, 77, β only
1a	**2c**	**3c**	16 h, 73, β only
1a	**2d**	**3d**	48 h, 60, β only
1a	**2e**	**3e**	24 h, 68, β only
xyl*f*-Series			
1b	**2b**	**4b**	12 h, 90, 0.2 : 1
1b	**2c**	**4c**	18 h, 75, 0.4 : 1
1b	**2d**	**4d**	24 h, 68, 0.5 : 1
ara*f*-Series			
1c	**2b**	**5b**	12 h, 86, 1 : 0.2
1c	**2c**	**5c**	12 h, 72, 1 : 0.1
1c	**2d**	**5d**	24 h, 65, 1 : 0.1
lyx*f*-Series			
1d	**2b**	**6b**	12 h, 85, α only
1d	**2c**	**6c**	12 h, 75, α only
1d	**2d**	**6d**	24 h, 61, α only
1d	**2e**	**6e**	24 h, 62, α only

the semi-empirical AM1 method. Various conformations of the products generated, along with the relative energies obtained at AM1 level, are illustrated in Table 1 in the supporting information‡. This enabled us to systematically sample the conformational space and take the most stable conformation to be subjected to geometry optimizations with the more reliable B3LYP method with the 6-31G(d) basis set. The relative reaction energies at the B3LYP/6-31G(d) level of theory are depicted in Fig. 1.

From Fig. 1, it can be observed that the difference in the relative reaction energies of α and β isomers of D-rib*f* is -10.3 kcal mol^{-1} which suggests that the β isomer is preferred over the α isomer. In contrast to these results the difference in the relative reaction energies of the α and β isomers of D-lyx*f* is about 15.0 kcal mol^{-1} which in turn suggests the formation of the α isomer over the β isomer. The differences in the relative reaction energies of α and β isomers for D-ara*f* and D-xyl*f* derivatives are 3.42 and -0.8 kcal mol^{-1}, respectively, which indicates that while the α isomer is more preferred in the case of D-ara*f*, the β isomer is preferred for D-xyl*f*. However such small differences in the reaction energies between the two isomers suggest the feasibility of the formation of both the products. Thus the computational results corroborate well with the observed experimental trends. All the DFT and

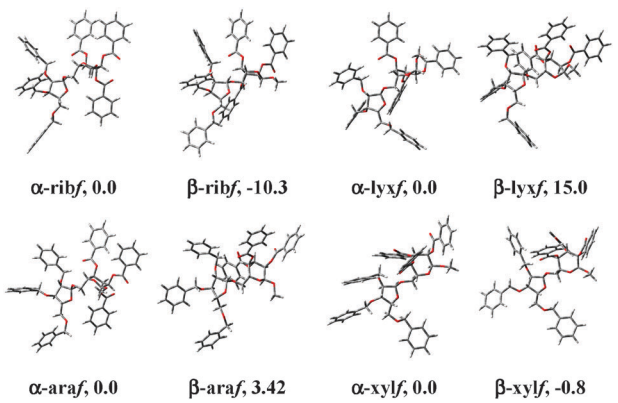
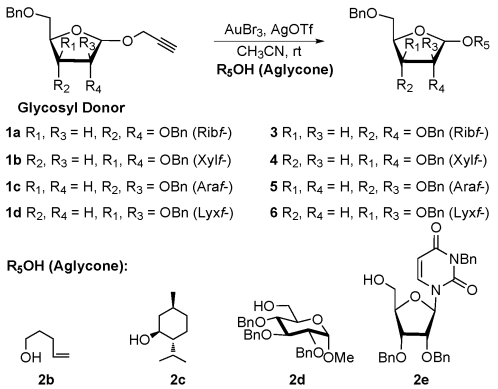


Fig. 1 Optimized structures of the products along with the relative reaction energies (in kcal mol^{-1}) at B3LYP/6-31G(d) level.



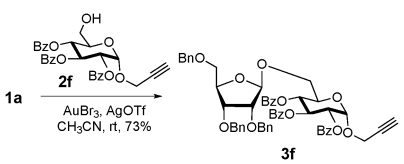
Scheme 2 Propargyl furanosides as glycosyl donors.

semiempirical calculations were done using the Gaussian program suite.[11]

To understand the generality of the observed facts, trans-furanosylations of glycosyl donors **1a** to **1d** with other aglycons were studied. Representative aglycons from aliphatic (**2b**), alicyclic (**2c**), carbohydrate (**2d**) and nucleosidic (**2e**) alcohols were considered (Scheme 2). Gratifyingly, D-rib*f* and D-lyx*f* donors **1a** and **1d** resulted in transglycosides **3b–3e** and **6b–6e** respectively in good yields with 1,2-*trans* diastereoselectivity (Table 1).[9] Similarly, D-xyl*f* and D-ara*f* donors **1b** and **1c** reacted well with aglycons **2b–2d** resulting in a diastereomeric mixture of 1,2-*trans* and 1,2-*cis* glycosides **4b–4d**, **5b–5d** (Table 1).[9]

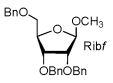
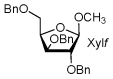
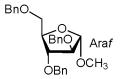
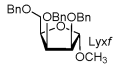
Owing to the observation that the transfuranosylations occur at room temperature, we anticipated that the chemoselective activation of propargyl containing aglycons could be possible.[6c] Accordingly, D-rib*f* donor **1a** was treated with propargyl pyranoside **2f** under the aforementioned conditions to obtain propargyl disaccharide **3f** due to the activation of the propargyl group of the rib*f* only (Scheme 3).

In continuation, we also explored the utility of methyl furanosides (**7–10**) as glycosyl donors and aglycons **2a–2c** under gold catalysis conditions.[6b] The initial reaction of methyl furanosides (**7–10**) with aglycon **2a** at room temperature did not afford the desired transglycosylated products (**3a**, **4a**, **5a** and **6a**) and hence we resorted to optimizing the reaction conditions. The optimum temperature was found to be 65 °C with acetonitrile as the solvent. Here again, we observed the same diastereoselectivities; for example, D-rib*f* (**7**) and D-lyx*f* (**10**) donors afforded **3a**, **6a** with 1,2-*trans* diastereoselectivity whereas D-xyl*f* (**8**) and D-ara*f* (**9**) resulted in glycosides **4a** and **5a** as a mixture of diastereomers.[9] Similar results were noticed when methyl furanosides (**7–10**) were reacted with other glycosyl acceptors **2b** and **2c** to furnish glycosylated products **3b**, **3c**, **4b**, **4c**, **5b**, **5c**, **6b**, **6c** in good yields (Table 2).[9]



Scheme 3 Chemoselective activation of propargyl furanosides in the presence of propargyl pyranoside.

Table 2 Methyl furanosides as glycosyl donors[a]

Aglycone	Glycosyl donor:  7	 8	 9	 10
	Time, Yield, α : β ratio			
2a	**3a** 24 h, 69%, β only	**4a** 24 h, 65%, 0.2 : 1	**5a** 24 h, 60%, 1 : 0.1	**6a** 24 h, 60%, α only
2b	**3b** 12 h, 90%, β only	**4b** 12 h, 91%, 0.2 : 1	**5b** 12 h, 85%, 1 : 0.2	**6b** 12 h, 89%, α only
2c	**3c** 16 h, 69%, β only	**4c** 18 h, 75%, 0.4 : 1	**5c** 12 h, 71%, 1 : 0.1	**6c** 12 h, 66%, α only

[a] Reaction conditions: $AuBr_3$, AgOTf, CH_3CN, 65 °C.

In conclusion, we found that propargyl/methyl furanosides can undergo transglycosylation reaction under gold(III) catalysed glycosylations conditions. We observed that D-rib*f* and D-lyx*f* give 1,2-*trans* selectivity and D-xyl*f* and D-ara*f* result in mixture of both 1,2-*cis* and 1,2-*trans* glycosides. Computational studies carried out at the B3LYP/6-31G(d) level corroborated well with experimental observations. The use of gold catalysed glycosidations for the synthesis of antigenic fragments of infectious microbes is currently under way.

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