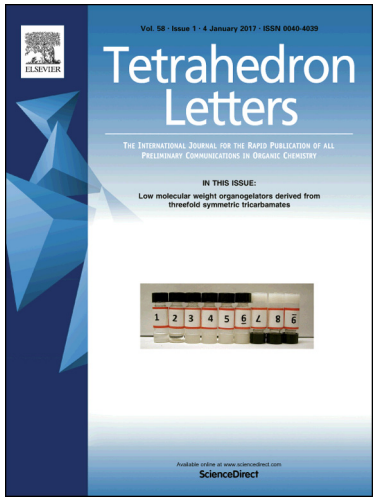


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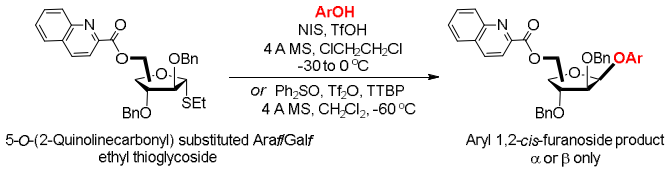


5-*O*-(2-Quinolinecarbonyl) substituted Ara*f*/Gal*f* ethyl thioglycoside

Aryl 1,2-*cis*-furanoside product
α or β only

# Stereoselective synthesis of aryl 1,2-*cis*-furanosides and its application to the synthesis of the carbohydrate portion of antibiotic hygromycin A

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**Abstract**: An efficient methodology for the synthesis of aryl 1,2-*cis*-furanosidic linkages has been developed with 2-quinolinecarbonyl (Quin) group substituted furanose ethyl thioglycosides as glycosyl donors. The method permits a wide range of phenol acceptors to be used, thus resulting in the formation of structurally diverse phenol furanosides in good to excellent chemical yields with complete 1,2-*cis* anomeric selectivity. The synthetic utility of the approach has been demonstrated by concise preparation of the carbohydrate portion of antibiotic hygromycin A.

*Keywords*: furanoside; hygromycin A; glycosylation; synthesis; thioglycoside; stereoselectivity

## Introduction

Hygromycin A is an antibiotic produced by several strains of *Streptomyces* and was first isolated in 1953.[1] It has been revealed that hygromycin A has a relatively broad spectrum of activity against Gram-positive and Gram-negative bacteria.[1a,b] In recent years, hygromycin A has held renewed appeal as it was found to be an effective agent for the control of swine dysentery, a mucohemorrhagic disease of economic importance to swine producers.[2] On the other hand, originally separated from a strain of *Streptomyces capreolus* in 1976, A201A is another structurally unique nucleoside antibiotic.[3] This compound was also found to be highly active against Gram-positive bacteria and most Gram-negative anaerobic bacteria.[4] The common structural feature of both natural products is that they possess the unique 1,2-*cis* glycosidic linkage between the furanose residue and the centeral phenol moiety. It is known that construction of 1,2-*cis* glycosides in a highly stereoselective manner is a significantly challenging task in synthetic carbohydrate chemistry.[5]

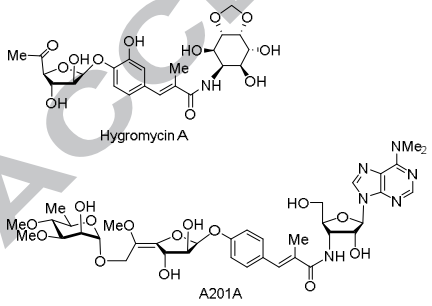
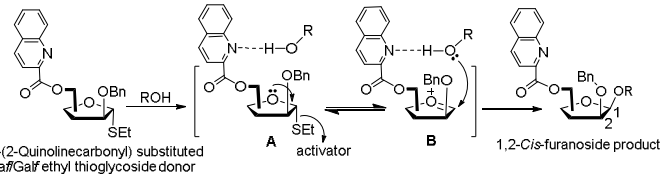



**Fig. 1.** Structures of hygromycin A and A201A.

In 1991, Ogawa and co-workers reported the first total synthesis of hygromycin A.[6] For the construction of the core phenol 1,2-*cis*-β-furanoside framework, they adopted 2,3-di-*O*-benzyl (Bn) protected furanose hemiacetal sugar as glycosyl donor to glycosylate with a suitable phenol derivative under standard Mistunobu reaction

conditions ($Ph_3P$, diethyl azodicarboxylate, THF). However, this coupling method provided the phenol furanoside product as an inseparable mixture of isomers with disappointing degree of stereocontrol (α:β = 4:5). In addition, Donohoe et al., by taking advantage of the same Mistunobu-type glycosylation but a 2,3-di-*O*-triisopropylsilyl (TIPS) ether protected furanose hemiacetal as donor instead, greatly elevated the stereoselectivity of the glycosylation to α:β = 1:9. Then, using this reaction as the key step, they accomplished the second total synthesis of hygromycin A.[7] More recently, this means was also employed by Yu et al. for the construction of the silimar aryl 1,2-*cis*-furanoside structure, thus leading to the first total synthesis of A201A.[8]




**Scheme 1.** 2-Quinolinecarbonyl-assisted 1,2-*cis*-furanosylation reaction.

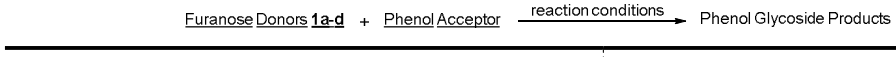
Recently, an efficient hydrogen-bond-mediated aglycone delivery (HAD) method was disclosed by Demchenko's group to stereoselectively synthesize a variety of 1,2-*cis*-pyranosides.[9] Based on such a concept, our group developed a novel 2-quinolinecarbonyl (Quin)-assisted 1,2-*cis*-furanosylation strategy for facile assembly of β-arabinofuranosides and α-galactofuranosides (Scheme 1).[10] The Quin group acting as a hydrogen bond acceptor displays a strong stereocontrolling capability in the glycosylation of both arabino- and galactofuranose thioglycoside donors with a wide scope of carbohydrate and non-carbohydrate acceptors. So, we sought to adopt this Quin-assisted 1,2-*cis*-furanosylation approach to the preparation of the relevant phenol 1,2-*cis*-furanosidic bond possessed by antibiotic hygromycin A and A201A. On the basis of these considerations, a set of Quin-containing furanose derivatives including 2,3-di-*O*-Bn-5-*O*-Quin substituted D- and L-thioarabinofuranoses **1a**[10a] and **1b**,[10a] and 2,3-di-*O*-Bn-5- or 6-*O*-Quin substituted D-thiogalactofuranoses **1c**[10c] and **1d**[10b] (Table 1) were prepared and used to condense with various phenol compounds. These thioglycosides have been proved by us to be excellent glycosylating reagents in the glycosylation with alcohol nucleophiles. Herein, we describe the development of a novel stereoselective glycosylation method for construction of phenol 1,2-*cis* furanosyl glycosides by use of thioglycosides **1a-d** and its application to the efficient preparation of the sugar fragment of hygromycin A.

**Results and discussion**

Initially, the glycosylation of thiofuranose donors **1a-d** with a variety of phenol acceptors was investigated. The results of these glycosylation reactions are summarized in Table 1. In the first instance, upon activation by the *N*-iodosuccinimide (NIS, 1.2 equiv)/trifluoromethanesulfonic acid (TfOH, 0.1 equiv) promoter system in dichloroethane ($ClCH_2CH_2Cl$) at −30 → 0 °C for 2 h, the coupling reaction between the D-arabinose donor **1a** and the simple phenol **2a** afforded the phenol glycoside **3a** in 86% yield as a only β product (Table 1, entry 1). The product stereochemistry was deduced by $^1H$ NMR spectroscopy in $CDCl_3$.[11] For the α-arabinofuranoside, $^3J_{H1,H2}$ is ~2.0 Hz, while for the β-arabinofuranoside, $^3J_{H1,H2}$ is ~5.0 Hz. Then, the influence of the substituent pattern of the phenol substrates on the reaction outcome was examined. As shown in Table 1, entries 2-5, the glycosylations of the diversely *para*-substituted phenol nucleophiles **2b-e** with donor **1a** gave the corresponding products **3b-e** in good to excellent yield and with exclusive β-stereocontrol. Furthermore, the couplings between **1a** and the *ortho*- or *meta*-substituted phenols **2f** and **2g** also led to high chemical yield and only β-stereoselectivity (Table 1, entries 6 and 7, respectively). However, in the case of the NIS/TfOH (cat.)-mediated

coupling of trisubstituted 2,4,6-tribromophenol **2h** to **1a**, only 45% yield of the desired glycoside **3h** was obtained. After screening several glycosylation conditions, we found that the reaction worked well under the promotion of diphenyl sulfoxide ($Ph_2SO$, 2.8 eq)/trifluoromethanesulfonic anhydride ($Tf_2O$, 1.4 eq)[12] at −60 °C in dichloromethane ($CH_2Cl_2$) for 2 h, furnishing the required aryl *O*-glycoside **3h** in an improved 66% yield as a single β-isomer. For the reactions of **1a** with the structurally more complex phenol derivatives **2i**[8] and **2j** (see Supporting Information), good to excellent yields were obtained as well, giving rise to the corresponding D-arabinofuranosides **3i** and **3j** as exclusive β-isomers in 90% and 85% yield, respectively. Importantly, these glycosides represent the characteristic carbohydrate subunits of hygromycin A and A201A, which would be benefit to the synthesis of these natural products and their analogues.

Table 1. Glycosylation of Furanose Thioglycosides **1a**-**d** with Phenol Compounds[a]




| entry | donor | acceptor | phenol glycoside product | yield[b] (α/β)[c] |
|---|---|---|---|---|
| 1 | **1a** | **2a** (R = H) | **3a** (R = H) | 86% (β) |
| 2 | **1a** | **2b** (R = Et) | **3b** (R = Et) | 89% (β) |
| 3 | **1a** | **2c** (R = $OCH_3$) | **3c** (R = $OCH_3$) | 65% (β) |
| 4 | **1a** | **2d** (R = Br) | **3d** (R = Br) | 90% (β) |
| 5 | **1a** | **2e** (R = CHO) | **3e** (R = CHO) | 55% (β) |
| 6 | **1a** | **2f** | **3f** | 81% (β) |
| 7 | **1a** | **2g** | **3g** | 80% (β) |
| 8[d] | **1a** | **2h** | **3h** | 45% (β)<br>66%[e] (β) |
| 9 | **1a** | **2i** | **3i** | 90% (β) |
| 10 | **1a** | **2j** | **3j** | 85% (β) |
| 11 | **1b** | **2b** (R = Et) | **3k** (R = Et) | 93% (β) |
| 12 | **1b** | **2d** (R = Br) | **3l** (R = Br) | 90% (β) |
| 13 | **1b** | **2e** (R = CHO) | **3m** (R = CHO) | 55% (β) |
| 14 | **1b** | **2k** (R = $NO_2$) | **3n** (R = $NO_2$) | 89% (β) |
| 15 | **1c** | **2b** (R = Et) | **3o** (R = Et) | 94% (α) |
| 16 | **1c** | **2d** (R = Br) | **3p** (R = Br) | 92% (α) |
| 17 | **1c** | **2e** (R = CHO) | **3q** (R = CHO) | 80% (α) |
| 18 | **1c** | **2k** (R = $NO_2$) | **3r** (R = $NO_2$) | 90% (α) |
| 19 | **1d** | **2b** | **3s** | 88%[f] (1:1) |

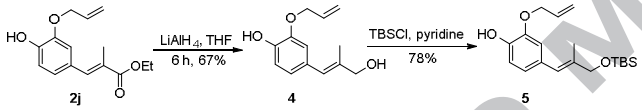
[a] Glycosylations were carried out with donor **1a**-**d** (1.3 equiv, 5 mM), acceptor (1 equiv), NIS (2.6 equiv)/TfOH (0.26 equiv), 4 Å molecular sieves (MS) in dichloroethane at −30 → 0 °C for 2 h unless otherwise noted. [b] Yield of isolated product based on the acceptor unless otherwise noted. [c] Determined by $^1$H NMR analysis of the corresponding reaction mixtures. [d] Glycosylation was performed with donor **1a** (1.0 equiv), acceptor **2h** (1.5 equiv), diphenyl sulfoxide ($Ph_2SO$, 2.8 equiv), trifluoromethanesulfonic anhydride ($Tf_2O$, 1.4 equiv), 2,4,6-tri-*tert*-butylpyrimidine (TTBP, 3 equiv) at −60 °C in dichloromethane for 2 h. [e] Yield was calculated based on the donor. [f] Combined yield of the α- and β-isomers.

To extend this methodology to the stereoselective synthesis of β-L-arabinofuranosyl phenol glycoside, we further studied the glycosylation of L-arabinofuranose donor **1b** with different phenol acceptors. It is found that **1b** exhibits similar reaction properties as that of its enantiomer **1a**. As shown by entries 11-14 in Table 1, each

condensation between **1b** and the phenol substrates **2b**, **2d**, **2e**, and **2k** was high yielding (55-93%) and β-selective (β only).

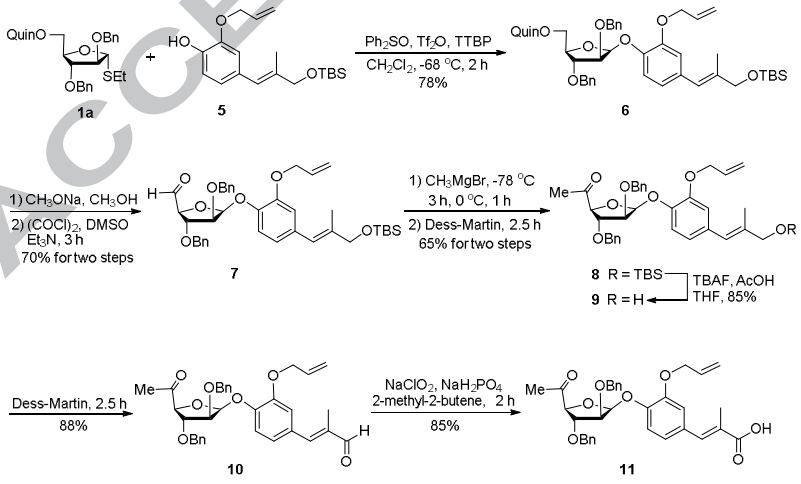
Finally, the reaction behaviour of the D-galactofuranose donors **1c**-**d** was tested. As displayed by entries 15-18 (Table 1), high yields and complete α-selectivity were also obtained in the glycosylation of the 5-*O*-Quin substituted donor **1c** with *para*-substituted phenol substrates. In contrast, the reaction between the 6-*O*-Quin substituted thioglycoside **1d** and 4-ethylphenol **2b** exhibited no stereoselectivity, resulting in the glycoside product **3s** as a separable mixture of isomers (α:β = 1:1) in an 88% combined yield. This is similar to the results that, in the galactofuranosylation of a variety of alcohol acceptors, the 5-*O*-substituted thiogalactofuranose donor generally provided higher stereoselectivity than the corresponding 6-*O*-substituted thiogalactofuranose donor counterpart.[10b] The difference in stereochemical outcome between both galactose donors is due to the probability that the hydrogen bond formed between the 6-*O*-Quin equipped donor **1d** and the acceptor is more flexible than that formed between the 5-*O*-Quin donor **1c** and the acceptor, thus leading to lower anomeric selectivity. The anomeric configuration of the formed D-galactofuranosidic bonds was also verified based on $^1$H NMR spectroscopy in $CDCl_3$. For the α-galactofuranoside anomer, the $^3J_{H1,H2}$ is 4.0~4.5 Hz, while, for the β-anomer, $^3J_{H1,H2}$ is 0~2.0 Hz.[13]

Having realized a practical approach to the synthesis of aryl 1,2-*cis* furanosyl glycoside, we planned to apply it as a key step for synthesizing the sugar portion of hygromycin A. Carboxylic acid **11** (Scheme 3), containing a core phenol 1,2-*cis* furanoside skeleton, was chosen as the target molecule.




**Scheme 2.** Preparation of aglycon **5**.

The aglycon part of **11** was first synthesized. As illustrated in Scheme 2, the readily available carboxylic ester **2j** was reduced with lithium aluminium hydride ($LiAlH_4$) in tetrahydrofuran (THF) for 6 h, affording alcohol **4** in 67% yield. Then, selective protection of the primary alcohol hydroxyl group of **4** with *tert*-butyldimethylsilyl (TBS) ether gave the desired phenol **5** (78% yield).




**Scheme 3.** Preparation of carboxylic acid **11**.

With the required aglycon building block in hand, we next turned our attention to the synthesis of **11**. As depicted in Scheme 3, upon activation by $Tf_2O/Ph_2SO$ at –68 °C in $CH_2Cl_2$ for 2 h,[14] the D-arabinofuranose donor **1a** was condensed with the phenol derivative **5** to give solely the β-monosaccharide glycoside **6** in 78% yield. The β-configuration of the newly formed arabinofuranosidic bond was clearly determined by the doublet for the anomeric signal of the Ara*f* unit ($\delta_{H1}$ = 5.633 ppm, d, $J_{H1/H2}$ = 4.8 Hz).[11] Removal of the 5-*O*-Quin group of **6** by treatment with sodium methoxide in methanol followed by Swern oxidation of the resulting alcohol afforded the corresponding aldehyde **7** in 70% yield over the two steps. Then, after reaction with Grignard reagent methylmagnesium bromide (MeMgBr) in THF at –78 °C and followed by oxidation with the Dess-Martin reagent, compound **7** was readily converted into methyl ketone **8** (65% yield, two steps from **7**). Selective cleavage of the TBS group of **8** by treatment with tetrabutylammonium fluoride (TBAF) buffered with HOAc in THF yielded free alcohol **9** in a good 85% yield. Finally, the stage was set to oxide this material to the target carboxylic acid product **11**. However, subjection of **9** to the well-studied TEMPO oxidation protocol[15] failed to generate the desired acid **11**. Instead, only a trace amount of aldehyde **10** was obtained. Pleasingly, successful conversion of **9** to **11** was achieved by a two-step procedure. Firstly, the hydroxyl group of **9** was oxided to aldehyde group by treatment of **9** under Dess-Martin conditions, giving rise to aldehyde **10** in 88% yield. Secondly, oxidation of **10** under Pinnick oxidation conditions ($NaClO_2$, $NaH_2PO_4$)[16] led to the formation of the expected acid **11** in 75% yield.

In conclusion, we have developed an efficient approach to the construction of the difficult-to-obtain phenol 1,2-*cis* furanosyl glycosidic linkages using a HAD strategy. The methodology was applied successfully to the short synthesis of the sugar fragment of hygromycin A. Further application of the method to the preparation of carbohydrates bearing an aryl 1,2-*cis* furanoside structure is currently underway.

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**A. Supplementary data**

Supplementary data associated with this article can be found, in the online version, at http:// .

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1. A approach to the construction of aryl 1,2-*cis*-furanosidic bonds is developed.
2. Aryl 1,2-*cis*-furanosides are synthesized using Quin-substituted thiofuranosides.
3. The method is demonstrated by preparation of the sugar portion of hygromycin A.