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N-Benzyl-2,3-oxazolidinone as a Glycosyl Donor for Selective α-Glycosylation and One-Pot Oligosaccharide Synthesis Involving 1,2-*cis*-Glycosylation

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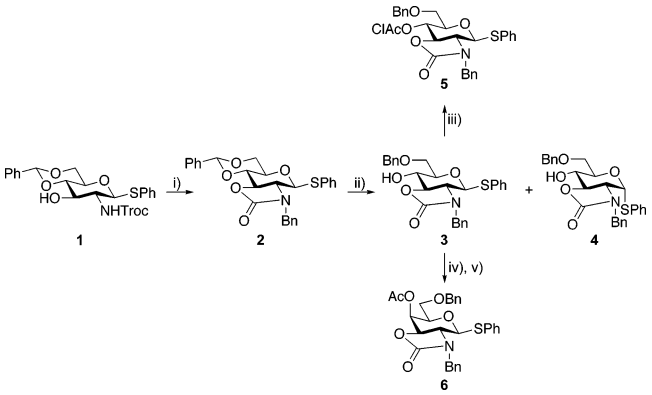
Routine oligosaccharide synthesis can become feasible pending the development of robust stereoselective glycosylations. In general, reasonable anomeric selectivities can only be obtained by extensive optimization of reaction conditions, such as solvent, temperature, and promoter, as well as leaving groups and protecting groups. To date, the stereoselective formation of 1,2-*cis* glycosides remains as the principal challenge in complex oligosaccharide synthesis.[1] In particular, the 1,2-*cis* stereoselective glycosylation for 2-amino-2-deoxy sugar has not progressed since Lemieux and Paulsen introduced an azido moiety at the 2-position as a nonparticipating group about 30 years ago.[2] In 2001, Kerns reported that a 2,3-*trans*-oxazolidinone, carrying glycosyl donor, possesses high α-selectivities.[3] Unfortunately, the use of this glycosyl donor has several disadvantages:[4] (1) significant side reactions include the sulfenylation and glycosylation of the nitrogen atom, and (2) requirement of at least 2 equiv of the activator phenylsulfenyl triflate. Furthermore, acetylation of the amino group significantly reduces the α-selectivities; in some cases, *β*-selectivity was observed.

Herein, we report on the use of *N*-benzyl-2,3-*trans* oxazolidinones (**5** and **6**) as novel glycosyl donors for the 1,2-*cis*-glycosylation for 2-amino-2-deoxy sugars. As shown in Scheme 1,

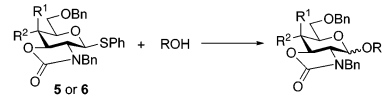
Scheme 1 [a]



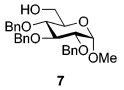
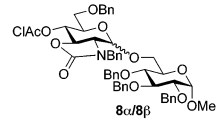
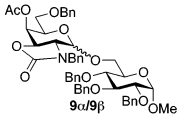
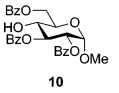
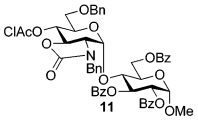
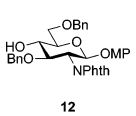
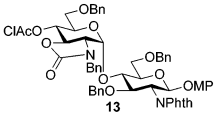
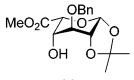
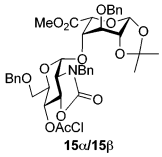
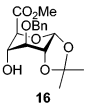
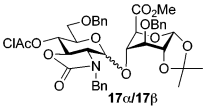
[a] (i) BnBr, NaH, DMF, 96%; (ii) Et_3SiH, BF_3·OEt_2, CH_2Cl_2, **3**, 72%, **4**, 11%; (iii) chloroacetic anhydride, pyridine, CH_2Cl_2, 99%; (iv) Tf_2O (2 equiv), pyridine (4 equiv), CH_2Cl_2, −40 to −20 °C; (v) NaOAc, DMF, 73% (2 steps).

the straightforward synthesis of **5** and **6** starts with the one-step conversion of the trichloroethyl carbamate protected GlcNAc derivative **1**,[3] using BnBr and NaH to the 2,3-*trans*-oxazolidinone derivative **2** (96% yield). Reductive benzylidene acetal ring opening under typical conditions using $Et_3SiH-BF_3$·OEt_2 gave **3** and **4** with a free hydroxy group at the 4-position. Interestingly, the configuration of the anomeric carbon was labile under acidic conditions,

Table 1. Stereoselectivites of Glycosylation Reactions Using the Novel Glycosyl Donor



5 R^1 = H, R^2 = ClAcO
6 R^1 = AcO, R^2 = H

entry	donor	ROH	product	conditions[a]	yield (%) α:β
1	**5**	 **7**	 **8α/8β**	A	31:37
				B	35:47
				C	80:8
2	**6**	**7**	 **9α/9β**	C	76:5
3	**5**	 **10**	 **11**	B	52 (α only)
4	**5**	 **12**	 **13**	B	54 (α only)
5	**5**	 **14**	 **15α/15β**	B	63:4
				C[b]	71 (α only)
6	**5**	 **16**	 **17α/17β**	C	71:4

[a] (A) AgOTf, PhSCl, DTBMP, CH_2Cl_2, rt; (B) *N*-(phenylthio)-ϵ-caprolactam, Tf_2O, CH_2Cl_2, rt; (C) AgOTf, PhSCl, DTBMP, toluene/1,4-dioxane (3:1), 0 °C to rt. [b] 1.6 equiv of the donor was used.

as previously reported by Crich and Oscarson.[5] Subsequently, **3** was converted either to glycosyl donor **5** via chloroacetylation or to galactosamine donor **6** via the triflate intermediate. With thioglycosides **5** and **6** in hand, our attention was focused on stereoselective glycosylations with these glycosyl donors.

The stereoselectivies of the glycosylations were investigated using primary alcohol **7** as the glycosyl acceptor. In general, highly reactive primary alcohols are not expected to exhibit high α-stereoselectivities. The results are listed in Table 1. Thioglycoside activation of **5** involving PhSOTf[6] or *N*-(phenylthio)-ϵ-caprolactam-Tf_2O[7] led to nonstereoselective glycosylations, affording both α and *β* products.[8] In contrast, the use of a mixture of toluene and

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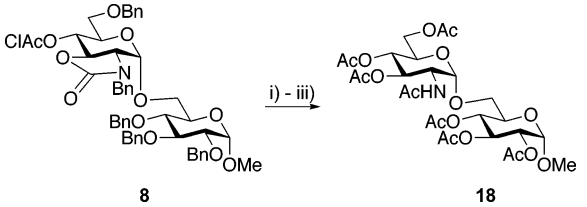
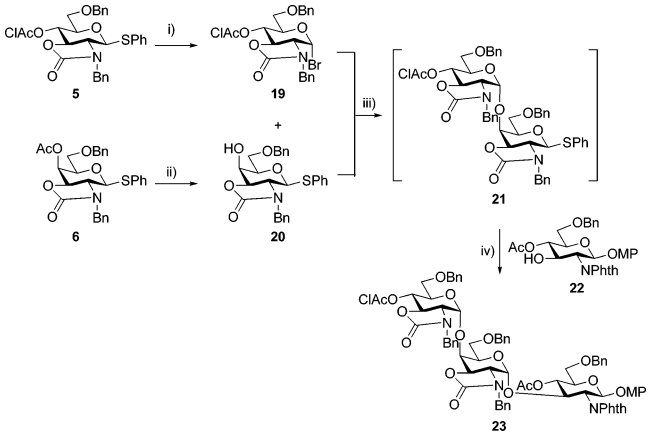
Scheme 2 [a]



8 **18**

[a] (i) 1 M NaOH, 1,4-dioxane; (ii) H_2, 20% $Pd(OH)_2/C$, 0.1 M HCl, dioxane, H_2O; (iii) Ac_2O, pyridine, 92% (3 steps).

Scheme 3 [a]



[a] (i) Br_2, CH_2Cl_2, 91%; (ii) NaOMe, MeOH/1,4-dioxane, 99%; (iii) AgOTf, MS4A, di-*tert*-butylmethylpyridine, toluene/1,4-dioxane (3:1); (iv) AgOTf, PhSCl, 81%.

dioxane at near room temperature[9] dramatically increased the α-selectivity. Under these reaction conditions, galactosamine donor **6** exhibited a slightly higher α-selectivity. This methodology using either conditions B or C of the glycosylation reaction was applied to various glycosyl acceptors. In the cases of the less-reactive secondary hydroxyl group in the 4-position of glucose **10** and glucosamine derivative **12** under condition B, complete α-selectivities were observed; the corresponding *β*-glycosides were undetectable after gel filtration of the crude mixture within the limits of 400 MHz ^{1}H NMR analysis. Moreover, α-selectivity was observed for the less-reactive secondary alcohol regardless of the solvent. Although the hydroxy group at the 4-position of glucosamine is known to be relatively unreactive, disaccharide **13** was obtained in good yield.[10] Similarly, high α-selectivities were observed for **15**α[11] and **17**α,[11] which are components of heparin, a drug for the prevention and treatment of thromboembolic disorders.[12]

As shown in Scheme 2, disaccharide **8**α was deprotected under basic conditions, followed by the concomitant removal of the *O*- and *N*-benzyl groups via hydrogenolysis. Acetylation of the unprotected disaccharide afforded **18** in overall 92% yield. Subsequently, the novel glycosyl donor was applied toward a one-pot oligosaccharide synthetic strategy.[13] Therefore, we proposed that glycosyl donor **5** can form two 1,2-*cis* glycosidic bonds in a one-pot operation (Scheme 3), where a component of the immune system stimulating *O*-specific polysaccharide from *Proteus mirabilis* O48 was chosen as the target molecule.[14]

The axial acetyl group of **6** was removed using standard procedures, without disruption of the strained oxazolodinone group to afford **20**. Bromide **19** was prepared from thioglycoside **5** in 91% yield. After activation of bromide **19** by AgOTf in the presence of di-*tert*-butyl-methylpyridine, then disaccharide **21** was activated by addition of excess amounts of AgOTf and PhSCl in the presence of the second acceptor **22**. Trisaccharide **23** was obtained, with complete α-selectivity in 81% yield, although Kerns reported the difficulty of activation of the 2,3-*trans*-oxazolidinone having disaccharide.[4a] To the best of our understanding, this is the first example of the preparation of two *cis* glycoside bonds in a one-pot operation.

In conclusion, we have demonstrated *N*-benzyl 2,3-*trans*-oxazolidinone having glycosyl donors exhibits high α-selectivities. Although at this moment, the origin of high α-selectivity is not clear, the glycosyl donors can be prepared in gram-scale, thus avoiding the use of triflyl azide necessary for the preparation of the 2-azido-2-deoxy sugar system or avoiding the low yields of the azido-nitration procedure. Furthermore, the 2,3-oxazolidinone can be cleaved under basic conditions. In regard to the preparation, glycosylation, and deprotection procedures, it is our belief that this novel donor can serve as an ideal glycosyl donor for 1,2-*cis* glycosidic bond formation. Furthermore, by using these novel glycosyl donors, the sequential two-step glycosylation reaction in a one-pot operation to form two *cis* bonds was successful. Application of such a donor to polymer-supported or automated oligosaccharide synthesis can also be promising because no severe low temperature is required for α-selectivity.[15] Further investigations of bioactive oligosaccharide synthesis using these donors are currently underway.

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Supporting Information Available: Preparation of new compounds and experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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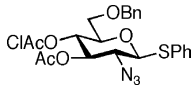
(10) When the azido donor, as indicated below, was coupled to **12** under condition B at −40 °C, both α and *β* glycosides were obtained in 24% and 10%, respectively.



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