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Synthesis of Azapyranosyl Thioglycoside: Novel Pseudo-disaccharide Having an Azasugar Residue at the Non-Reducing End

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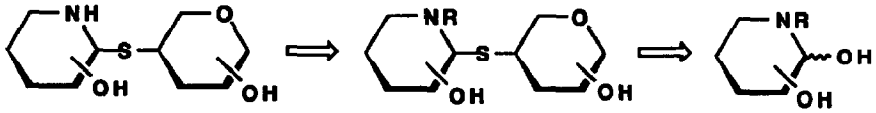
Abstract: The first synthesis of azapyranosyl pseudo-disaccharide was described. Glycosidation of *N*-Boc-5- amino-5-deoxy-D-arabinose with *N*-acetyl-6-thio-D-glucosaminide in the presence of TsOH gave the corresponding 1,2-*cis* linked thioglycoside exclusively. The interglycosidic linkage was proved to be stable enough for the deprotection of *N*-Boc group by TFA.

Recently, many azasugars (pseudo-sugars with nitrogen in the ring) have shown to be remarkable inhibitory activity, due to the strong affinity for the carboxylate group in the active site of glycosidase,[1] against glycosidases which hydrolyze the glycosidic linkage of hexopyranoses having the same configurations as those of azasugars.[2] Oligosaccharide of this type is expected to be more specific inhibitor than monosaccharide analog. Up to now, synthesis of oligosaccharides having 1-deoxy-azaaldose[3a-c] and 2-deoxy-azaketose[3d] at the reducing end have been reported. However, azapyranosyl oligosaccharide, even a disaccharide, has not been synthesized, because *O*-glycoside of *N*-free azasugar is easily hydrolyzed in an aqueous solution.[4] In this paper, a disaccharide having azasugar residue at the non-reducing end was first synthesized using thioglycosidic linkage.

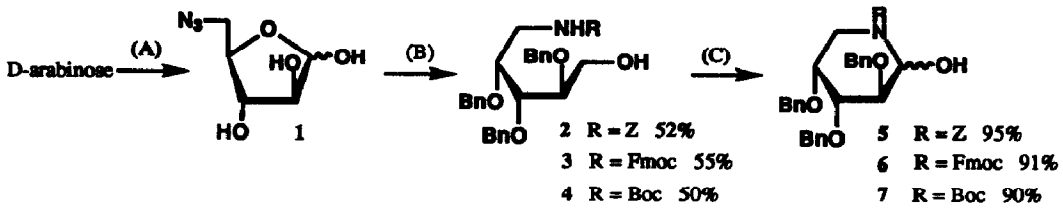
Our strategy based on the glycosidation of *N*-protected azasugar derivative with sugar thiol and successive deprotection is shown in the following retrosynthetic description (Scheme 1).



Aza-pyranosyl disaccharide R = Protective group

Scheme 1

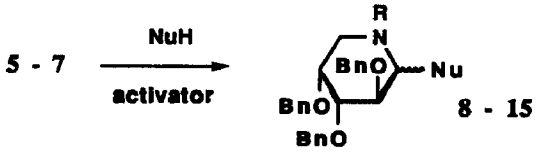
Coupling condition was examined using 2,3,4-tri-*O*-benzyl-*N*-protected-5-amino-5-deoxy-D-arabinoses **5**, **6**, and **7**, which were synthesized *via* 5-azido-5-deoxy-D-arabinose **1** from D-arabinose as shown in Scheme 2. Reaction of their 1-acetates with simple alcohols and thiols in CH_2Cl_2 at room temperature in the presence of TMSOTf (1 equiv) gave the corresponding glycosides **8** - **12** (method A in Table 1). Under these conditions, *N*-Z (benzyloxycarbonyl) and *N*-Fmoc (9-fluorenylmethyloxycarbonyl) groups were stable but *N*-Boc (t-butoxycarbonyl) group was unstable. In the case of the *N*-Boc donor **7**, the direct coupling proceeded smoothly in the presence of TsOH (1 equiv) as a catalyst, giving the glycosides **13** -**15** in satisfactory yields (method B).



(A) 1. TrCl, Py. 2. Ac_2O, Py. 3. 70% AcOH aq. 4. MsCl, Py. 5. NaN_3, DMSO 6. NaOMe, MeOH
(B) 1. $NaBH_4$, MeOH 2. TrCl, Py. 3. BnBr, NaH, DMF 4. 70% AcOH aq. 5. $LiAlH_4$, THF then H_2O, ZCl or FmocCl or Boc_2O (C) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2

Scheme 2

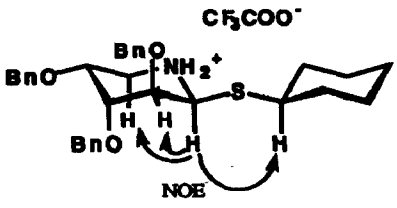
Table 1. Glycosylation with N-protected-5-amino-5-deoxy-D-arabinoses.



Entry	Donor	Method[a]	Acceptor (NuH)	Yield(%)	β : α[c]	Product
1	5	A	$(CH_3)_3CCH_2OH$	quant.	1 : 0	8 R = Z , Nu = $OCH_2C(CH_3)_3$
2	5	A	EtSH	quant.	3 : 1	9 R = Z , Nu = SEt
3	6	A	EtSH	79	2.8 : 1	10 R = Fmoc , Nu = SEt
4	6	A	$C_6H_{11}SH$	73	3.1 : 1	11 R = Fmoc , Nu = SC_6H_{11}
5	7	A[b]	EtSH	40	3.8 : 1	12 R = Boc , Nu = SEt
6	7	B	$C_6H_{11}SH$	72	7.3 : 1	13 R = Boc , Nu = SC_6H_{11}
7	7	B	$C_6H_{11}OH$	73	1 : 0	14 R = Boc , Nu = OC_6H_{11}
8	7	B	MeOH	88	1 : 0	15 R = Boc , Nu = OMe

a A : 1. Ac_2O, Py. 2. TMSOTf (1.1equiv), acceptor (3 equiv), MS4A, CH_2Cl_2, r. t.
B : TsOH H_2O (1 equiv), acceptor (3 equiv), CH_2Cl_2, r. t.
b TMSOTf (0.3 equiv).
c Ratios were determined by intensities of ^{1}H-NMR signals of H-1.[5]

The *N*-Boc group of the thioglycoside was successfully deprotected, while *N*-Z and *N*-Fmoc groups were unsuccessful[6] due to decomposition of the glycosides. Treatment of the *N*-Boc thioglycoside **13** with 2 : 1 (v / v) TFA - CH_2Cl_2 at room temperature for 1 h gave *N*-free glycoside[7] **16** quantitatively as a single anomer. The thioaminal structure of **16** is supported by ^{13}C-NMR (δ 60.04 C-1 in $CDCl_3$).[8] The NOE observed between H-1 and H-5 in ^{1}H-NMR of **16** indicates *C1* conformation and 1,2-*cis*-glycoside. The conformational change of the azapyranose ring is due to the positive charge of the ring nitrogen atom. The change of anomeric ratio seems to indicate the anomerisation of **13** or **16** under the deprotection conditions.



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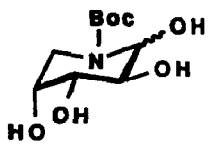
The above mentioned glycosylation was applied to synthesis of a pseudo-disaccharide. 5-Azide **1** was converted to *N*-Boc aminal **17** in good yield by catalytic hydrogenation in the presence of Boc_2O. Condensation of the aminal **17** with a 6-thiosugar[9] **18** in the presence of TsOH (1 equiv) at room temperature for 5-10 min gave a 1,2-*cis* linked thioglycoside **19** exclusively in 80% yield, which was converted to the pentaacetate[7] **20** quantitatively. The conformation of the azapyranose ring was confirmed to be *1C* by small coupling constants between H-4 and two H-5 protons. Therefore, the $J_{1',2'}$ value of 4.61 Hz indicates a 1,2-*cis* glycosidic linkage. The ^{13}C-NMR spectrum of pentaacetate **20** in $CDCl_3$ shows two signals of thioaminal C1' (δ 61.60 and 60.95) due to amide mesomerism[4] of the *N*-Boc group (a 1 : 1 mixture of *E*- and *Z*-isomers). Stereoselectivity of this glycosidation seems to be controlled by anomeric effect.[10] De-*O*-acetylation of the thioglycoside **19** give **21** in 99% yield. The *N*-Boc group of **21** was cleaved smoothly by 2 : 1 (v / v) TFA - CH_2Cl_2 at room temperature for 1 h to give an azapyranosyl disaccharide[7] **22** quantitatively. A large coupling constant between H-4 and one of two H-5 protons indicates a conformational change of the azapyranose ring from *1C* to *C1*. The conformational change was similar to that from **13** to **16**. Thus, a disaccharide having azasugar residue at the non-reducing end was first synthesized by linking the glycon and aglycon part through a thioglycosidic linkage. Very recently, an alternative possibility to synthesize a pseudosaccharide having azasugar at the non-reducing end was reported using amidine linkage.[11] These methods may provide a new route to develop the specific inhibitor of *endo*-glycosidases. The inhibitory activity of **22** are currently being evaluated.



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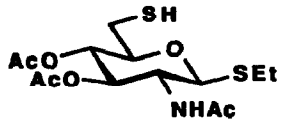

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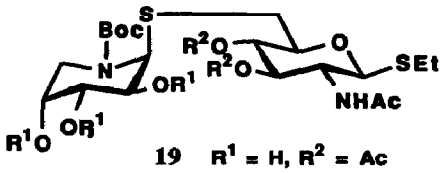
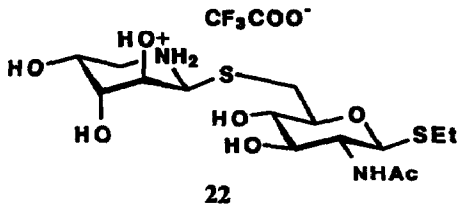


19 R^1 = H, R^2 = Ac
20 R^1 = R^2 = Ac
21 R^1 = R^2 = H



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5. For example, the ^{1}H-NMR spectrum of thioglycoside **11** shows four signals of H-1 because both the α- and β-anomers (1 : 3.1) are composed of a 1 : 1 mixture of *E*- and *Z*-isomers due to amide mesomerism of the Fmoc group. The anomeric configuration was confirmed by coupling constants of H-1 (α : $J_{1,2}$ < 0.3 Hz, β : $J_{1,2}$ = 5.61 Hz).
6. Catalytic hydrogenation of **8** gave 2, 3, 4-tri-*O*-benzyl-1-deoxy derivative in good yield. Compound **9** didn't react at all under the same condition. Treatment of compound **10** and **11** with TBAF in THF gave a common product, tri-*O*-benzylated 1, 2-didehydropiperidine derivative, quantitatively. Treatment of *N*-Boc *O*-glycoside **14** with TFA-CH_2Cl_2 gave a pyridine derivative.
7. For all new compounds satisfactory analytical and spectral data were obtained. Selected spectral data for **16**: ^{1}H-NMR ($CDCl_3$): δ 4.56 (br s, H-1), 3.42 (dd, $J_{4,5e}$ = 4.62 Hz, $J_{5a,5e}$ = 11.87 Hz, H-5e), 3.31 (dd, $J_{4,5a}$ = 11.55 Hz, H-5a), 3.10 (m, S-CH<). **20**: ^{1}H-NMR (nitrobenzene-d5 at 393K): δ 6.45 (br d, $J_{1',2'}$ = 4.61 Hz, H-1'), 6.12 (br d, $J_{2,NH}$ = 9.24 Hz, N*H*), 5.18 (dd, $J_{4,5}$ = $J_{3,4}$ = 9.41 Hz, H-4), 5.06 (d, $J_{1,2}$ = 10.23 Hz, H-1), 4.50 (br d, $J_{5a,5e}$ = 14.84 Hz, H-5'e), 4.29 (ddd, $J_{2,3}$ = 9.74 Hz, H-2), 3.91 (m, H-5), 3.70 (br d, H-5'a), 2.99-2.79 (m, H-6a,6b, S-C*H*$_2$CH$_3$), 2.16, 2.14, 2.12, 2.09, 2.08, 2.07 (each s, Ac), 1.61 (s, t-Bu), 1.36 (t, S-CH$_2$C*H*$_3$). **22**: ^{1}H-NMR (D_2O): δ 4.66 (d, $J_{1,2}$ = 11.00 Hz, H-1), 4.57 (br s, H-1'), 4.17-4.09 (m, H-2',4'), 3.91 (br s, H-3'), 3.34 (dd,$J_{4',5'e}$ = 4.62 Hz, $J_{5'a,5'e}$ = 12.05 Hz, H-5'e), 3.20 (d, $J_{6a,6b}$ = 13.52 Hz, H-6a), 3.15 (d, H-6b), 3.11 (dd, $J_{4',5'a}$ = 10.56 Hz, H-5'a), 2.71-2.57 (m, S-C*H*$_2$CH$_3$), 1.92 (s, Ac), 1.15 (t, S-CH$_2$C*H*$_3$).
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