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Stereoselective Synthesis of O-(2-Azido-2-deoxy-α-D-galactopyranosyl)-L-serine and -L-threonine Derivatives by Using the Catalytic Amount of Active Acidic Species

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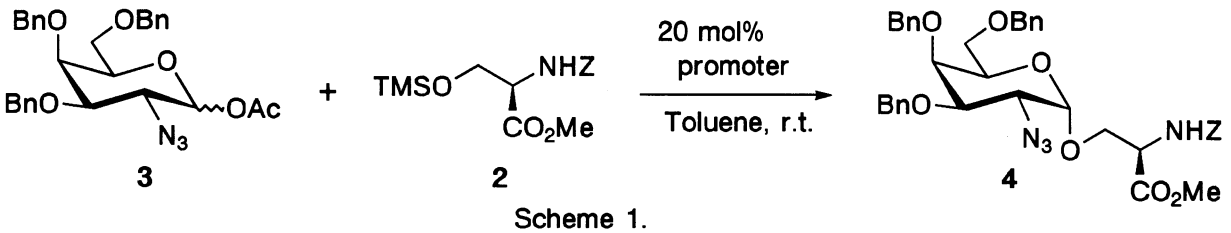
In the presence of a catalytic amount of $SnCl_3(ClO_4)$ or $SiCl_3(ClO_4)$, O-(2-azido-2-deoxy-α-D-galactopyranosyl)-L-serine and -L-threonine are stereoselectively synthesized in excellent yields from 1-O-acetyl-2-azido-2-deoxy-3,4,6-tri-O-benzyl-D-galactopyranose and trimethylsilylated L-serine or L-threonine, respectively.

Glycoproteins and glycooligopeptides perform important functions in cell differentiation and in the regulation of cell growth. Though it is essential to obtain the chemically pure materials in the investigation of the function of the glycoproteins, their preparations by means of biological methods are difficult. Therefore, establishment of efficient chemical synthetic methodology of these glycoproteins is strongly desired.

Stereoselective formation of the α-glycosidic linkages between the derivatives of 2-azido-2-deoxy-D-galactopyranose (precursors of the 2-acetamide-2-deoxy-D-galactopyranosyl residue) and the protected amino acids (L-Ser or L-Thr) have been reported by way of a variety of glycosylation methods.[1] However, there are some problems such as instability of the glycosyl donners, poor yield of the desired α-glycosides, and toxic character of the promoters. In addition, more than one equimolar amount of heavy metal activators such as silver salts or mercury salts are generally required for the completion of the desired glycosylations, and there are few examples to prepare the α-galactopyranosyl L-serine or L-threonine in high yields by using a catalytic amount of promoter. Based on the above results, development of a useful glycosylation method by a catalytic process was investigated.

Recently, we have reported an efficient method for the preparation of 2-amino-2-deoxy-β-D-glucopyranosides and galactopyranosides starting from 1,3,4,6-tetra-O-acetyl-2-(2,2,2-trichloroethoxycarbonylamino)-2-deoxy-β-D-glucopyranose or galactopyranose and alkyl trimethylsilyl ethers by using a catalytic amount of tin(II) trifluoromethanesulfonate.[2] Then, glycosylation reaction of 1,3,4,6-tetra-O-acetyl-2-azido-2-deoxy-β-D-galactopyranose (**1**) with benzyloxycarbonyl (Z) protected L-serine methyl ester trimethylsilyl ether (**2**) was attempted first, but the corresponding galactoside was not obtained at all, probably because of the inactivity of **1**. Next, 1-O-acetyl-2-azido-2-deoxy-3,4,6-tri-O-benzyl-D-galactopyranose (**3**)[3] was employed as a starting substrate and the glycosylation reaction with **2** was carried out under the same reaction conditions. As a result, the desired galactoside (**4**) was obtained in 75% yield (α/β = 80 / 20). Several other promoters were screened by taking the above mentioned reaction of **3** with **2** as a model (see Scheme 1; Table 1).

It was found that the corresponding galactoside was obtained in good yield with high stereoselectivity when

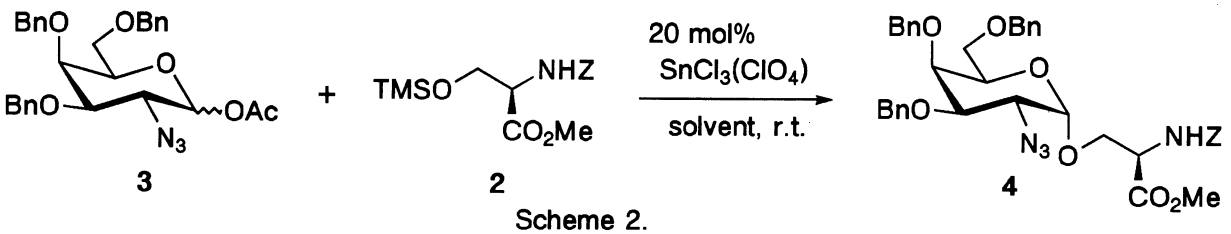


Scheme 1.

Table 1. Effect of promoters

Entry	Promoters	Time / h	Yield / %	α / β
1	$Sn(OTf)_2$	50	75	80 / 20
2	$SnCl(ClO_4)$	50	20	80 / 20
3	$Sn(ClO_4)_2$	50	50	71 / 29
4	$SnCl_3(OTf)$	12	99	83 / 17
5	$SnCl_3(ClO_4)$	5	>99	88 / 12
6	$SiCl_3(ClO_4)$	5	>99	88 / 12
7	$TrClO_4$	9	98	82 / 18

$SnCl_3(ClO_4)$ or $SiCl_3(ClO_4)$, generated in situ from tin(IV) chloride or silicon(IV) chloride and silver perchlorate, was employed as a catalyst.[4] Furthermore, after screening various solvents, the use of benzene as a solvent gave the best result (see Scheme 2; Table 2).



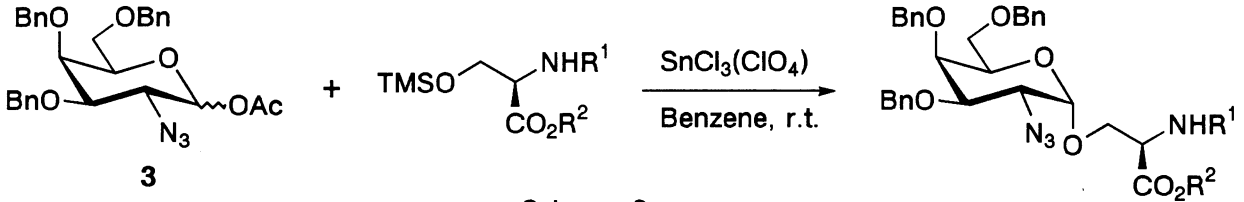
Scheme 2.

Table 2. Effect of solvents

Entry	Solvents	Time / h	Yield / %	α / β
1	Toluene	5	>99	88 / 12
2	Benzene	5	>99	89 / 11
3	CH_2Cl_2	10	98	82 / 18
4	$MeNO_2$	1	96	65 / 35
5	MeCN	5	89	40 / 60
6	Et_2O	5	97	80 / 20

Pure α- and β-anomers of **3** were respectively employed under the above reaction conditions in order to explore whether the ratio of α- and β-isomers of produced galactosides was dependent on the ratio of α- and β-anomers of **3** or not. The same α/β-selectivity was observed in both reactions. This result suggested that both the reactions proceeded via S_N1 process through the common oxocarbenium cation.

Since it is necessary to remove distinctively the protective groups of amino, hydroxyl, and carboxyl groups in the produced galactosides, several L-serine derivatives protected by other protective groups were screened (see Scheme 3; Table 3).[5]



Scheme 3.

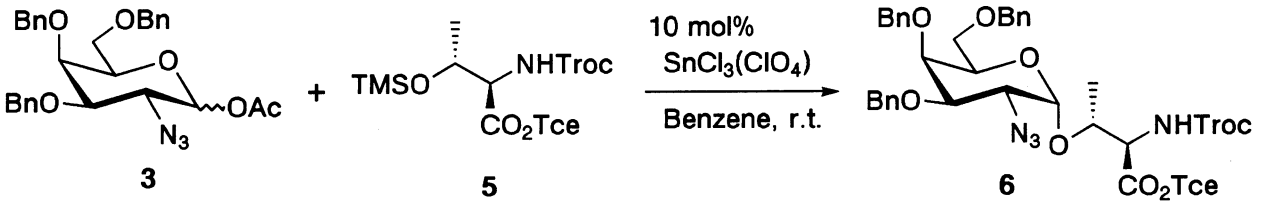
Table 3. Synthesis of O-(2-azido-2-deoxy-D-galactopyranosyl)-L-serine

Entry	R^1	R^2	Catalytic amount / mol%	Yield / %	Time / h	α / β
1	Z [a]	Me	20	>99	5	89 / 11
2	Troc [b]	Me	20	>99	1	90 / 10
3	Troc	Tce [c]	20	>99	1	92 / 8
4	Troc	Tce	10	>99	1	92 / 8
5	Troc	Tce	5	98	5	95 / 5

a) Z = benzyloxycarbonyl. b) Troc = 2,2,2-trichloroethoxycarbonyl. c) Tce = 2,2,2-trichloroethyl.

In every case, the corresponding α-galactosides were prepared in excellent yields with high stereoselectivities,[6] even when 5 mol% of the catalyst was used. It should be noted that amino and carboxyl protective groups are stable during removal of benzyl groups and can be simultaneously removed by Zn reduction in the case of Troc protected L-serine Tce ester.

The above procedure was further applied to the glycosylation reaction of **3** with Troc protected L-threonine Tce ester trimethylsilyl ether (**5**). As a result, the corresponding α-galactoside (**6**) was obtained exclusively (see Scheme 4).



Scheme 4. **Yield 95% (α only)**

A typical experimental procedure for the preparation of **6** is as follows; a solution of $SnCl_4$ (0.03 mmol) in benzene (0.1 ml) was added to a solution of silver perchlorate (0.03 mmol) in benzene (6 ml) at room temperature, and the mixture was shielded from a light and stirred for 1 h. To this mixture was added a solution of 1-O-acetyl-2-azido-2-deoxy-3,4,6-tri-O-benzyl-D-galactopyranose (**3**; 0.3 mmol) and **5** (0.36 mmol) in benzene (4 ml) at room temperature. After stirring the mixture for 3 h, aqueous sodium hydrogen carbonate was added. Usual work up and separation by TLC afforded **6** (95%).

Thus, highly stereoselective synthesis of O-(2-azido-2-deoxy-α-D-galactopyranosyl)-L-serine and -L-threonine is successfully carried out by using the catalytic amount of active acidic species generated from $SnCl_4$ or $SiCl_4$ and $AgClO_4$.

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4) We have already reported an efficient glycosylation method using these promoters. T. Mukaiyama, T. Takashima, M. Katsurada, and H. Aizawa, *Chem. Lett.*, **1991**, 533; T. Mukaiyama, M. Katsurada, and T. Takashima, *ibid.*, **1991**, 985.

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6) In the case when C-2 position is protected with acyl group, β-anomers are formed predominantly because of neighboring effect as mentioned in the previous paper.[2] However, when C-2 position is substituted by azido group, β-anomers are scarcely formed due to the disappearance of neighboring effect. In stead, α-anomers are formed predominantly because β-side is blocked by sterically hindered perchlorate anion in the intermediate oxocarbenium cation.

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