

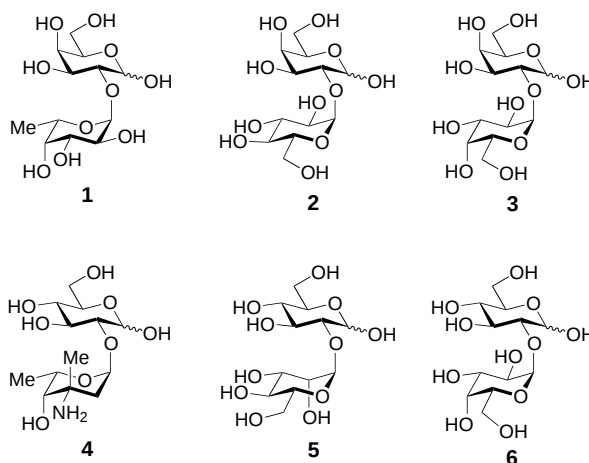
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Synthesis of Biologically Potent $\alpha 1 \rightarrow 2$ -Linked Disaccharide Derivatives via Regioselective One-Pot Protection – Glycosylation**

Cheng-Chung Wang, Jinq-Chyi Lee, Shun-Yuan Luo, Hsin-Fang Fan, Chin-Ling Pai, Wei-Chieh Yang, Lung-Dai Lu, and Shang-Cheng Hung*

*Dedicated to Professor Chun-Chen Liao
on the occasion of his 60th birthday*

$\alpha 1 \rightarrow 2$ -Linked disaccharides are key subunits of numerous biologically potent oligosaccharides, antigens, antibiotics, glycoproteins, and glycolipids. For example, the tumor antigen Globo H,^[1] ABH blood groups,^[2] and human milk oligosaccharides^[3] contain α -L-Fuc(1 $\rightarrow$ 2)-D-Gal (**1**) as a common component. α -D-Glc(1 $\rightarrow$ 2)-D-Gal (**2**) is a structural element of glycoproteins isolated from the body wall of leeches.^[4] α -D-Gal(1 $\rightarrow$ 2)-D-Gal (**3**) is found as the disaccharide repeating unit of *Streptococcus pneumoniae* type 15 antigen.^[5] Vancomycin, a significant glycopeptide antibiotic against gram-positive bacteria, has a disaccharide moiety **4**, which consists of $\alpha 1 \rightarrow 2$ -linked vancosamine with D-glucopyranose.^[6] α -D-Man(1 $\rightarrow$ 2)-D-Glc (**5**) is a typical constituent in the cell membrane of halophilic bacteria.^[7] The glycolipids extracted from *Lactobacillus casei* A.T.C.C. 7469 are composed of α -D-Gal(1 $\rightarrow$ 2)- α -D-Glc(1 $\rightarrow$ 1)-glycerol lipid **6** as the major com-



ponent.^[8] Given the importance of these disaccharide motifs with $\alpha 1 \rightarrow 2$ linkages, there is a need to develop a highly selective protection^[9] of hexopyranosides to generate a free hydroxy group at C2 for their synthesis. To tackle this problem, we describe herein a highly regioselective benzyl or allyl protection of hexopyranosides to the corresponding 2-hydroxy compounds by means of very mild, acid-catalyzed, reductive etherification of their O-trimethylsilylated derivatives with a variety of aldehydes.^[10] Finally, we show their applications in the regioselective one-pot protection – glycosylation to prepare these biologically potent $\alpha 1 \rightarrow 2$ -linked disaccharide derivatives.

The one-pot synthesis of the trimethylsilyl ether **8** from methyl α -D-glucopyranoside **7** in 74% yield was carried out through a combination of 4,6-O-benzylidenation and 2,3-di-O-silylation. Triethylsilane-reductive O3-etherification of **8** with various aryl and α,β -unsaturated aldehydes in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) as the catalyst successfully afforded the corresponding 2-hydroxy compounds **9–15**. Excellent selectivity and yields were observed in comparison with known methods for the regioselective introduction of acyl or alkyl groups in D-glucopyranosides at O3 (Table 1).^[11] Under these acidic conditions, it was observed that the 4,6-O-benzylidene acetal of **8** was not hydrolyzed or opened, and that the double bonds of allyl ethers **14** and **15** were not further reduced. The regiochemistry of **9–15** was determined through the ^1H and $^1\text{H},^1\text{H}$ COSY NMR spectra: H2 was correlated with the proton of the free hydroxy group as well as with H1. The high selectivity is perhaps induced not only by the steric hindrance between the anomeric methoxy group and the 2-OTMS group, but also by the inductive effect of two anomeric oxygen atoms which causes a decrease in the nucleophilicity of O2.

We studied the regioselective etherification in a variety of O-trimethylsilylated pyranosides (Table 2). The highlights include 3-O-benzoylation of different protected D-glucopyranosides and α,α' -trehalose, and 6-O-benzoylation of β -cyclodextrin as well as of the D-galactopyranosyl derivatives. The 4,6-O-isopropylidene ketal **16**, α -allyl ether **18**, and β -D-thioglucopyranoside **20** were selected to examine the compatibility of substituted groups at the O4, O6, and anomeric positions, and the corresponding 3-OBn compounds **17**, **19**,

[*] Dr. S.-C. Hung, C.-C. Wang, S.-Y. Luo, H.-F. Fan, C.-L. Pai
Institute of Chemistry, Academia Sinica
Taipei 115 (Taiwan)
Fax: (+886) 2-2783-1237
E-mail: chung@chem.sinica.edu.tw
J.-C. Lee, W.-C. Yang, L.-D. Lu
Department of Chemistry, National Tsing Hua University
Hsinchu 300 (Taiwan)

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Table 1. Trimethylsilyl trifluoromethanesulfonate activated triethylsilane-reductive O3-etherification of **8** with a variety of aryl and α,β -unsaturated aldehydes.^[a]

Entry	R	T [°C]	t [h]	Product	Yield [%]
1	Ph	−78	0.5	9	94
2	4-OMePh	−78	0.5	10	91
3	3,4-(OMe) ₂ Ph	−78	3	11	87
4	4-ClPh	−78	4	12	77
5	2-naphthyl	−78	2	13	81
6	(<i>E</i>)-MeHC=CH	−86	6.5	14	68
7	(<i>E</i>)-PhHC=CH	−86	6.5	15	87

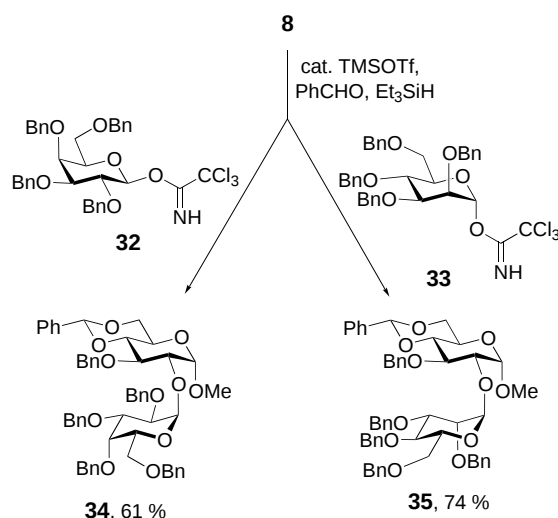
[a] Reagents and conditions: a) PhCH(OMe)₂, CSA, TMSCl, Et₃N, 74%; b) cat. TMSOTf, RCHO, Et₃SiH, CH₂Cl₂. TMS = trimethylsilyl; CSA = camphorsulfonic acid; Tf = trifluoromethanesulfonyl.

Table 2. Trimethylsilyl trifluoromethanesulfonate activated triethylsilane-reductive benzylation of various O-trimethylsilylated sugars with benzaldehyde at −78 °C.

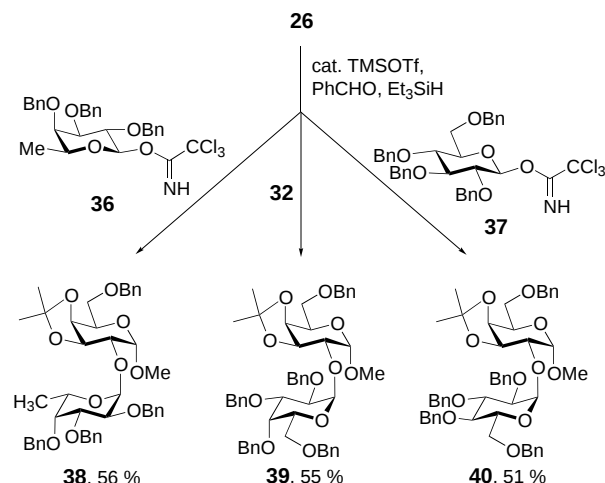
Entry	Silylated sugar	Product	Yield [%]
1			75
2			87
3			86
4			87
5			62
6			96
7			95
8			92
9			91

and **21**, respectively, were obtained in good yields (Table 2, entries 1–3). A similar phenomenon was observed in the α,α' -trehalose derivative **22**: the 3,3'-di-O-benzylated product **23** was produced in high yield under the standard conditions (Table 2, entry 4). No 2-OBn regioisomer was detected in any of the above cases. However, the corresponding 2,3-diols (entries 1–3) and 2,2',3,3'-tetraol (entry 4), which result from the hydrolysis of the bis-OTMS functionalities owing to prolonged reaction times, were isolated in 5–10% yields, which cause a slight drop in the overall yield. Regioselective benzylation of cyclodextrin molecules at various hydroxy groups is a big challenge for synthetic chemists.^[12] Interestingly, we found that the O-trimethylsilylated β -cyclodextrin **24**^[13] successfully delivered the corresponding 6-OBn compound **25** in 62% yield after recrystallization from methanol (Table 2, entry 5). Finally, the 3,4-O-isopropylidene-D-galactopyranosyl sugars **26** and **30** (Table 2, entries 6–9) also displayed excellent regioselectivity as expected to provide the 2-hydroxy compounds **27–29** and **31**, respectively, in very high yields compared to etherifications under basic conditions.^[14]

To the best of our knowledge, the regioselective one-pot protection–glycosylation strategy of carbohydrate molecules has not been studied to date. Since TMSOTf was successfully used as the catalyst in the reductive etherification and it was often the reagent of choice in the coupling reactions of sugars, we investigated this methodology further to prepare the α -linked disaccharide units in one-pot syntheses. The perbenzylated D-galacto (**32**), D-manno (**33**), L-fuco (**36**), and D-glucopyranosyl (**37**) trichloroacetimidates^[15] were selected as glycosyl donors. TMSOTf-catalyzed triethylsilane-reductive benzylation of the D-glucopyranosyl sugar **8** followed by coupling with **32** and **33**^[16] gave the expected α -disaccharides **34** and **35** in 61% and 74% yields, respectively (Scheme 1). Similarly, regioselective one-pot O6-benzylation and O2-glycosylation of **26** with **36**, **32**, or **37** led to the desired products **38** (56%), **39** (55%), or **40** (51%), respectively (Scheme 2). Their α configurations were determined from the coupling constants of the anomeric protons. Compounds **34**,



Scheme 1. Regioselective one-pot benzylation–glycosylation of **8** with the glycosyl donors **32** and **33** to form the α -linked disaccharides **34** and **35**, respectively.



Scheme 2. Regioselective one-pot benzoylation-glycosylation of **26** with the glycosyl donors **36**, **32**, and **37** to form the α -linked disaccharides **38**, **39**, and **40**, respectively.

35, **38**, **39**, and **40** are the protected versions of biologically potent disaccharides **6**, **5**, **1**, **3**, and **2**, respectively.

In conclusion, we have successfully developed a highly regioselective benzyl and allyl protection of hexopyranosides, and demonstrated their applications in the synthesis of biologically potent α 1 $\rightarrow$ 2-linked disaccharide derivatives in a regioselective one-pot protection-glycosylation.

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- [16] **General Procedure:** A mixture of the trimethylsilyl ether (1.0 equiv), freshly dried molecular sieves (3 Å, 1 mg per 1 mg trimethylsilyl ether), benzaldehyde (1.2 equiv), triethylsilane (1.2 equiv), and dichloromethane (8.5 mL per 1 mmol trimethylsilyl ether) was stirred at room temperature for 30 min under nitrogen. The mixture was cooled to -78°C , trimethylsilyl trifluoromethanesulfonate (0.1 equiv) was slowly added, and the reaction was monitored by TLC. After the starting material was totally consumed, a solution of the glycosyl trichloroacetimidate^[15] (1.2 equiv) in dichloromethane (5 mL per 1 mmol glycosyl donor) and trimethylsilyl trifluoromethanesulfonate (0.3 equiv) were added successively, the system was gradually warmed up to -40°C , and the mixture was stirred at the same temperature overnight. The reaction was quenched with saturated aqueous sodium bicarbonate, and the aqueous phase was extracted with ethyl acetate (3 $\times$). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography to give the expected disaccharide. The yields are summarized in Schemes 1 and 2.