A Fundamentally New, Simple, Stereospecific Synthesis of Oligosaccharides Containing the β-Mannopyranosyl and β-Rhamnopyranosyl Linkage

György Hodosi* and Pavol Kováč

NIDDK, Section on Carbohydrates, LMC
National Institutes of Health
Bethesda, Maryland 20892-0815

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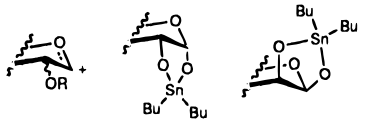
The important role of oligosaccharides in biological processes[1] has been recognized for a long time. Consequently, synthetic oligosaccharides have become indispensable probes for the life sciences.[2] Methods for the chemical synthesis of oligosaccharides are based on a two-step process: The first comprises activation of the anomeric center to generate a glycosyl donor, and the second is its transfer to a glycosyl acceptor. The stereochemical outcome of the reaction depends on complex stereoelectronic effects as well as the presence or absence of groups at O-2 in the glycosyl donor capable of neighboring group participation.[3] Except for rare cases, when the coupling of a glycosyl donor and a glycosyl acceptor occurs as an almost entirely S_N2 process,[4] the reaction of the glycosyl donor involves the formation of the oxocarbenium ion (**1**). Thus, the *non*stereospecificity of glycosylation is virtually inherent in the method.



1 **2** (*e.g.* α-gluco) **3** (*e.g.* β-manno)

Syntheses of 1,2-*trans*-linked oligosaccharides are relatively easy, but not the highly stereoselective syntheses of their 1,2-*cis*-linked counterparts. Most difficult are syntheses of β-mannosides and β-rhamnosides.[5] Both the anomeric effect, which favors the formation of the α-mannopyranosyl linkage, and the formation of **1** during the transition state of the reaction are largely responsible for this unfavorable situation. Efforts aimed at overcoming these difficulties continue, and some new approaches have recently been introduced.[6] Nevertheless, there is still a need for more efficient methods of glycosylation not involving the formation of the oxocarbenium ion.

We have now discovered that 1,2-*O*-*cis*-stannylene acetals of sugars are powerful nucleophiles capable of displacing, *via* the S_N2 process, good leaving groups in carbohydrates. This constitutes a fundamentally new method for the glycosylation of carbohydrates in that it does not involve the formation of the oxocarbenium ion as an intermediate of the process, and makes specific protection of hydroxyl groups in the glycosyl donor unnecessary.[7,8] Here, stereospecific formation of the 1,2-*cis*-glycosidic linkage occurs because 1,2-*O*-stannylene acetals of sugars favor the *cis*-arrangement around the anomeric center (**2**, **3**).[9] Therefore, we propose to call the procedure "the glycosylation *via* locked anomeric configuration". Accordingly, when the stannylene derivatives[10] prepared from L-rhamnose or D-mannose were treated with carbohydrates bearing the (trifluoromethyl)sulfonyl (triflyl) group, the 1,2-*cis*-oligosaccharides[11] formed could be isolated in 57−88% yields (Table 1).

Table 1. Reaction Conditions Applied and Yields Obtained

Nu[a] equiv	El[b] equiv	prod	yield (%)	solvent	temp (°C)	reaction time	salt/ equiv
7/4.5	**5**/1	**8**	88	DMF	−5	80 min	CsF/6
7/4.5	**9**/1	**10**	78	DMF	25	2.5 h	CsF/6
11/4	**5**/1	**13**	40	DMF	0, 25	4 h, 10 h	
11/3	**5**/1	**13**	57	CH_3CN	25	20 h	Bu_4NF/1
11/6	**9**/1	**18**	40	DMF	25	5 d	
11/6	**9**/1	**18**	52	DMAA	25	3 d	
11/6	**9**/1	**18**	59	DMSO	25	2 d	
12/5	**5**/1	**14**	75	CH_3CN	25	14 h	Bu_4NF/1
12/6	**9**/1	**19**	67	DMF	25	18 h	CsF/6

[a] Nucleophile. [b] Electrophile.

Table 2. Characteristic Data for Newly Synthesized Substances[a]

compd	mp (°C)	$[\alpha]_D$[b] deg	δ_{H-1^I}/ $J_{1,2}$ Hz	$\delta_{H-1^{II}}$ /$J_{1,2}$ Hz	δ_{C-1^I}/ $J_{C,H}$ (Hz)	$\delta_{C-1^{II}}$/ $J_{C,H}$ (Hz)
5			5.26/3.7		97.7	
6[c,d]			5.16/3.2		97.4	
8[e]	150−151	+127	5.24/3.7	4.52/<1	97.2/172.7	99.1/157.8
10		+142	5.15/3.4	4.48/<1	96.9/170.0	100.2/158.0
13		+30	5.22/3.3	4.47/<1	97.0/175.9	101.1/158.3
14		+16	5.22/3.7	4.40/<1	96.9/175.7	100.9/158.6
16		+56	5.17/3.5	6.06/2.0	96.7/172.9	90.3/177.2
18[e]	106−107	+104	5.13/3.6	4.58/<1	96.8/176.1	100.5/156.3
19		+83	5.12/3.7	4.50/<1	97.0/171.0	99.3/157.7

[a] Unless stated otherwise, the NMR spectra were measured at 300 (^{1}H) and 75 (^{13}C) Mz for solutions in $CDCl_3$. [b] Optical rotations were measured for solutions in $CHCl_3$, $c \approx 1$. [c] NMR spectra were measured in C_6D_6. [d] δ_{HCO} 7.58; δ_{HCO} 160.0. [e] Crystalized from ethanol.

Reactions of 1,2-*O*-stannylene acetals of sugars with secondary triflates of carbohydrates occur, as expected, with inversion of configuration at the activated center in the electrophile. Thus,

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(6) (a) Ito, Y.; Ogawa, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1087. (b) Stork, G.; Kim, G. *J. Am. Chem. Soc.* **1992**, *114*, 1087−1088. (c) Baresi, F.; Hindsgaul, O. *J. Am. Chem. Soc.* **1991**, *113*, 9376. (d) Stork, G.; La Clair, J. *J. Am. Chem. Soc.* **1996**, *118*, 247−248.
(7) 1-*O*-Alkylation with alkyl halides of 1,2-*O*-stannylene complexes has been previously used to synthesize simple alkyl β-D-mannopyranosides (ref 8). Unlike the cases described herein, the stannylene complex used was that of 3,4,6-tri-*O*-benzyl-D-mannose. Under the conditions described (ref 8), we have not observed (TLC) formation of oligosaccharides from 1,2-*O*-stannylene complexes and nonanomeric halogeno sugars.
(8) (a) Dessinges, A.; Olesker, A.; Lukacs, G.; Thang, T. T. *Carbohydr. Res.* **1984**, *126*, C6−C8. (b) Srivastava, V. K.; Schuerch, C. *Tetrahedron Lett.* **1979**, 3269−3272.
(9) (a) We verified this (ref 9b) by treatment of 1,2-*O*-stannylene acetals of various sugars with acetic anhydride and isolation of the 1,2-*O*-*cis*-per-*O*-acetyl derivatives in 85% to virtually theoretical yields. (b) Hodosi, G.; Kováč, P. *Abstracts, XVIII International Carbohydrate Symposium*, Milano, Italy, July 21−26, 1996; International Carbohydrate Organization: Milano, Italy, 1966; p 394.
(10) The acetals are prepared as described in a typical experiment above. Their solubility during the reaction is maintained by addition of a phase-transfer salt (Table 1). The preferred solvent for glycosylation is acetonitrile. However, the solubility of many stannylene acetals in it decreases, and the reaction rate, particularly that of the much less reactive secondary triflates, is impractically slow in that solvent. Therefore, we also used DMF, DMSO, and DMAA (Table 1).
(11) (a) The stereochemistry of the newly formed glycosidic linkage was deduced from the chemical shift for H-1^{II} and from the $J_{C-1,H-1}$, found in the NMR spectra (Table 2). (b) All new compounds gave correct microanalyses and/or exhibited ^{1}H, ^{13}C NMR, and mass spectral characteristics in accord with their structures (*cf*, Table 2).

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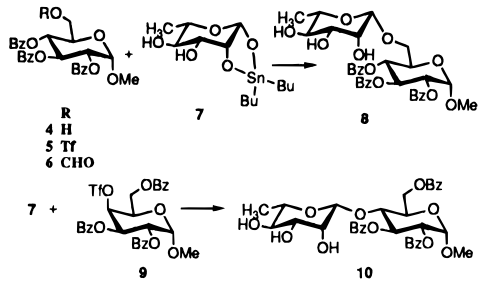
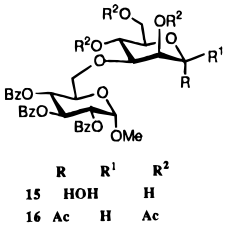
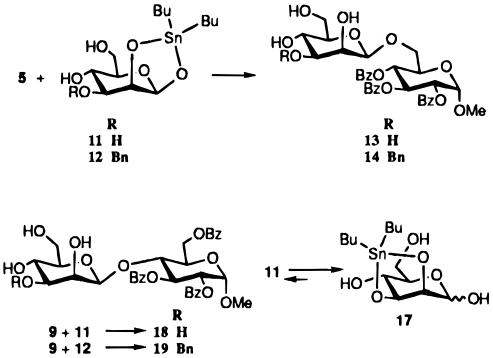
treatment of **7** with the known[12] methyl 2,3,6-tri-*O*-benzoyl-4-*O*-triflyl-D-galactopyranoside (**9**) gave the corresponding β-(1→4)-linked disaccharide **10** in 78% yield. The best yield reported thus far[13] for the formation of the β-L-Rha-(1→4)-Glc linkage was 43%.



Reactions of **7** in DMF were fast and gave virtually one product. Conversely, the analogous acetal of D-mannose (**11**) was much less reactive, and side reactions were observed during the reaction time required for the conversion to be complete. For example, formation of formates, such as **6**, was observed when DMF was the solvent (Table 1). Also, ether-linked disaccharides, such as **15**, were occasionally formed. The latter was characterized *via* the α-per-*O*-acetyl derivative **16**. A

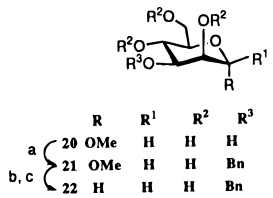


plausible explanation for the formation of **15** is the competitive reaction at the equatorial O-3 in D-mannose whose reactivity, compared to the O-3 in **11**, was increased by the isomerization of the acetal **11** (→ **17**) during the reaction. The side reactions could be minimized by conducting the same reaction in acetonitrile, but the reaction was much slower. Here, formation of **6** could be completely eliminated, and **13** could be isolated in 57% yield.



The presumed isomerization **11** → **17** during the conversion **5** + **11** → **13** suggested that the yield of **13** could be improved by the use of the 1,2-*O*-stannylene acetal of a 3-*O*-protected D-mannose, where such isomerization cannot occur. Indeed, when each of the triflates **5** and **9** was treated with the 1,2-*O*-stannylene acetal of 3-*O*-benzyl-D-mannose **12**, obtained from 3-*O*-benzyl-D-mannose (**22**; Scheme 1),[14] the β-(1→6)- and the β-(1→4)-linked disaccharides **14** and **19** were obtained in the respective yields of 75% and 67%.

Scheme 1[a]



[a] Conditions: (a) Bu_2SnO, anhydrous MeOH, reflux, 2 h; BnBr, DMF, CsF, 25 °C, 16 h, 84%. (b) Ac_2O, AcOH, catalytic H_2SO_4, 25 °C, 3 h, 94%. (c) anhydrous MeOH, catalytic NaOMe, 25 °C, 3 h, 95%.

Treatment in DMF of the much less reactive secondary triflate **9** with **11** gave the β-D-mannose-(1→4)-linked disaccharide **18** in 40% yield only. However, the reaction was very selective: only traces of a byproduct (an analog of **15**?) were formed. On the other hand, the formation of the β-(1→4)-linked disaccharide **18** was very slow, and some of the starting material(s) decomposed during the long reaction time. By changing the solvent, the yield of **18** could be increased to 59% (Table 1). It is worth noting that the same linkage was recently synthesized *via* a newly developed procedure,[6d] but in a yield of only 12%.[15,16]

In a typical experiment, a mixture of L-rhamnose (0.713 g, 3.92 mmol) and dibutyltin oxide (0.877 g, 3.52 mmol) in anhydrous methanol (25 mL) was stirred at 60 °C until a clear solution was obtained (∼1.5 h). CsF (0.714 g, 4.7 mmol) and toluene (5 mL) were added, and the mixture was concentrated. The residue, after having been kept at 50 °C, 0.2 Torr, for 2 h to assure dryness, was dissolved in DMF (5 mL), molecular sieves (4 Å, 0.5 g) were added, and the solution was cooled to −5 °C. After addition of **5** (0.5 g, 0.79 mmol), the mixture was stirred vigorously at −5 °C for 80 min, and concentrated. The residue was triturated with acetonitrile, the resulting suspension was filtered through a pad of Celite, solids were washed with acetonitrile, and the combined filtrate was concentrated. Chromatography of the residue gave **8** (0.45 g, 88%).

Preliminary attempts to synthesize other oligosaccharides containing 1,2-*cis*-glycosidic linkages (such as those containing α-gluco- or α-galactopyranosyl linkages) from $1_{ax},2_{eq}$-*O*-stannylene acetals indicate that those are much more complex processes.

One of the outstanding features of the new method is that specific blocking of hydroxyl groups in the glycosyl donor is not required. Moreover, examples we have shown of the use of the partially protected 1,2-*O*-stannylene acetal of D-mannose (**22**) indicate the potential the new method offers for the sequential construction of complex, higher oligosaccharides.

Acknowledgment. Authors dedicate this work to Professor János Kuszmann and thank Dr. Cornelis P. J. Glaudemans for his help and keen interest.

Supporting Information Available: An experimental example for preparation of compound **18** with analytical data (2 pages). See any current masthead page for ordering and Internet access instructions.

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(13) van Steijn, A. M. P.; Kamerling, J. P.; Vliegenthart, J. F. G. *J. Carbohydr. Chem.* **1992**, *11*, 665−689.
(14) 3-*O*-Benzyl-D-mannose was prepared as shown in the accompanying formulas **20**−**22**.
(15) A 77% yield of the same linkage was obtained in a different laboratory (ref 16) by the internal aglycon delivery method. Since the method described herein utilizes readily made acetals of unprotected sugars, the yields achievable in these two ways cannot be fairly compared.
(16) Baresi, F.; Hindsgaul, O. *Can. J. Chem.* **1994**, *72*, 1447−1465.