Synthesis of (6*R*,7*R*)-D-*gluco*-L-*gulo*-6,7-dodecodiulose-(6,2),(7,11)

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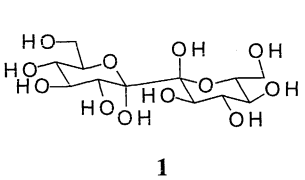
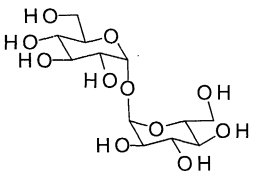
(6*R*,7*R*)-D-*gluco*-L-*gulo*-6,7-dodecodiulose-(6,2),(7,11) was synthesized from 3,4,6-tri-*O*-benzyl-1-stannyl-D-glucal via stereospecific addition reaction of lithioglucal to 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone.

Many kinds of mono-, di-, oligo-, polysaccharides, and their glycoconjugates (glycolipids and glycopeptides) are widely distributed in nature. However, for a long time these carbohydrates were generally regarded solely as energy storage vehicles and structural units in cells. While the expansion of glycotechnology and glycobiology has continued to progress at a rapid pace, nowadays it has been well recognized that carbohydrates play important roles in biological phenomena, and also govern a wide range of biological recognition phenomena. Recently, there has been much attention paid to manipulating various saccharides as a means of finding suitable glycosidase inhibitors with therapeutic application. In particular, α-glycosidase inhibitors have been implicated to be useful for treating diabetes or HIV. We also focused on these types of medicines constructed from derivatives of 1-deoxysugars of disaccharides such as sucrose, lactose, trehalose, maltose, cellobiose, and their analogues, especially the anomeric deoxy C-C bonded derivatives of trehalose. However, few efficient methods for the synthesis of anomeric deoxy C-C bonded derivatives of trehalose have been reported. Therefore, we tried to develop a synthetic methodology for anomeric deoxy C-C bonded derivatives of trehalose (**2**) or pseudo disaccharide analogues. In this paper, we would like to describe a stereoselective synthesis of (6*R*,7*R*)-D-*gluco*-L-*gulo*-6,7-dodecodiulose-(6,2),(7,11) (**1**) as a model synthetic route of anomeric deoxy C-C bonded disaccharide derivatives.

Starting materials, stannyl glucal **3**[1] and 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone (**4**),[2] were prepared according to reported procedures. As shown in Scheme 1, treatment of **4** with a lithioglucal generated from **3** by the action of *n*-BuLi gave a coupling product **5** as the only isomer in 71% yield. We expected that the configuration of the 6-hydroxy group in **5** was

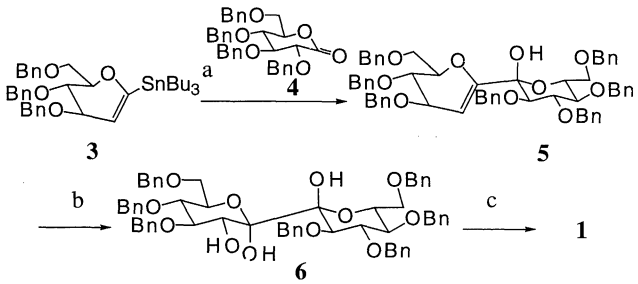


1



Trehalose (**2**)

axial since methoxymethyl lithium addition reaction with **4** gave only 6-axial-hydroxyl isomer as reported.[3] Without determining the anomeric configuration at this stage, **5** was subjected to dihydroxylation with *N*-methylmorpholine-*N*-oxide using catalytic amounts of OsO_4, to yield a triol **6** as one isomer. Finally, all benzyl groups in **6** were hydrogenolized using 10% Pd on carbon as a catalyst to give a deoxy disaccharide **1**, which has a direct bond between each anomeric position.



(a) *n*-BuLi / THF, -78°C, then **4**, 71%
(b) 5% OsO_4, *N*-methylmorpholine-*N*-oxide / THF - H_2O, 96%
(c) H_2, 10% Pd on carbon / THF, 43%

Scheme 1.

Considering the configuration of **1**, four stereoisomers are possible through glucal addition reaction to the gluconolactone and successive *cis*-dihydroxylation of the obtained glucal.

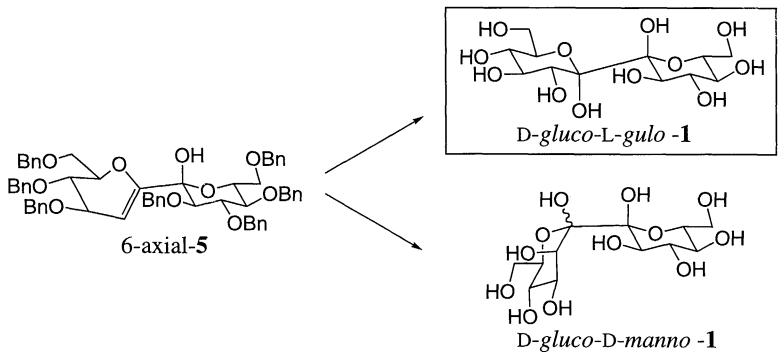


Figure 1. Possible configurations of **1**.

However, the reaction of lithioglucal **3** with gluconolactone **4** should proceed kinetically to give 6-axial hydroxy compound **5**, and successive *cis*-dihydroxylation of glucal **5** with OsO_4 may yield two 6-axial products, D-*gluco*-L-*gulo*-**1** and D-*gluco*-D-*manno*-**1**, after equilibration. (Figure 1) As a matter of fact, the ^{13}C NMR spectrum[4] revealed the structure of a compound obtained to be symmetrical, and the configurations of the hydroxy groups of the compound were determined to be 6-axial, 7-axial, and 8-equatorial. Among the two possible isomers, D-*gluco*-L-*gulo*-**1** and D-*gluco*-D-*manno*-**1**, the D-*gluco*-L-*gulo* compound (6-axial, 7-axial, and 8-equatorial) has a symmetrical structure. Therefore, it became obvious that lithioglucal addition to **4** proceeded stereospecifically to give 6-axial **5** as expected. Then, 6-axial **5** was dihydroxylated stereoselectively, mainly by the steric effect of the 3-benzyloxy group on the glucal moiety, to give 6-axial, 7-axial, 8-equatorial **6**. Thus, we could obtain **1**[4] in a stereocontrolled manner.

By analogy, using lithiated 3,4-dihydro-2*H*-pyran derivatives such as galactal, or 2,3-dihydrofuran derivatives in place of glucal, and using other sugar lactones in place of gluconolactone, these successive reactions should be applicable for preparation of other anomeric deoxy C-C bonded pseudo sugar analogues.

References and Notes

1 P. Lesimple, J.-M. Beau, G. Jaurand, and P. Sinaÿ, *Tetrahedron Lett.*, **27**, 6201 (1986).

2 a) H. Kuzuhara and H. G. Fletcher, Jr., *J. Org. Chem.*, **32**, 2531 (1967). b) T. D. Perrine, C. P. J. Glaudemans, R. K. Ness, J. Kyle, and H. G. Fletcher, Jr., *J. Org. Chem.*, **32**, 664 (1967).

3 M. Shiozaki, *J. Org. Chem.*, **56**, 528 (1991).

4 The spectroscopic data of **1** are as follows: IR (KBr) 3378(br), 1414, 1077, 1054 cm^{-1}; ^1H NMR (CD_3OD, 270 MHz) δ 4.86 (10H, broad), 3.84 - 3.65 (8H, m), 3.42 (4H, t, J = 9.2 Hz); ^{13}C NMR (CD_3OD, 270 MHz) δ 99.1, 75.6, 74.0, 72.8, 70.7, 61.8; high-resolution mass spectrum (FAB) *m/z* 381.1016 [$(M+Na)^+$; calcd. for $C_{12}H_{22}O_{12}Na$, 381.1009].