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Stereoselective synthesis of α- and β-*C*-glucosides via radical cyclization with an allylsilyl tether. Control of the stereoselectivity by changing the conformation of the pyranose ring

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Abstract

An efficient method for preparing both 1α- and 1β-*C*-glucosides having a 3-hydroxypropyl group at the anomeric position via a radical cyclization reaction with an allylsilyl tether was developed. The stereoselectivity of the radical cyclization can be controlled by the conformation of the pyranose ring, which is effectively manipulated by the hyroxyl protecting groups.

In recent years, we have been working to develop novel efficient D-*myo*-inositol 1,4,5-trisphosphate (IP_3, **1**) receptor ligands, which are highly useful for proving the mechanism of IP_3-mediated Ca^{2+} signaling pathways (Fig. 1).[1] During the course of our synthetic study using the D-glucose structure as a mimic of *myo*-inositol in IP_3,[2] we designed the *C*-glucoside trisphosphates **2** and **3** as potential IP_3 receptor ligands. In this communication, we describe an efficient stereoselective synthesis of β-*C*-glucoside **4** and α-*C*-glucoside **5**, which are useful intermediates for the synthesis of our target molecules **2** and **3**, via a radical cyclization reaction with an allylsilyl tether as the key step.

Because of the unique biological activities of *C*-glycosides, considerable effort has been devoted to developing practical methods for their preparation.[3] The use of radical reactions is one of the most efficient methods for constructing *C*-glycosidic bonds, and a number of studies have been reported using these reactions.[3,4] We planned to develop a novel procedure for introducing a C3 unit stereoselectively at both the 1α- and 1β-positions of D-glucose via the radical cyclization reaction with an allylsilyl group as a temporary connecting tether.[5] Scheme 1 shows our synthetic plan. We chose the phenyl β-seleno-D-glucopyranosides **6** and **7**, which have an allylsilyl tether on the 2-hydroxyl group, as the substrates for the radical reaction. We expected the stereoselectivity in the radical cyclization to change, depending

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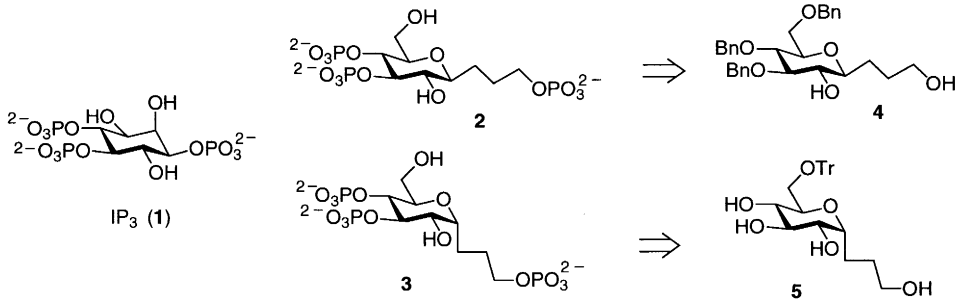
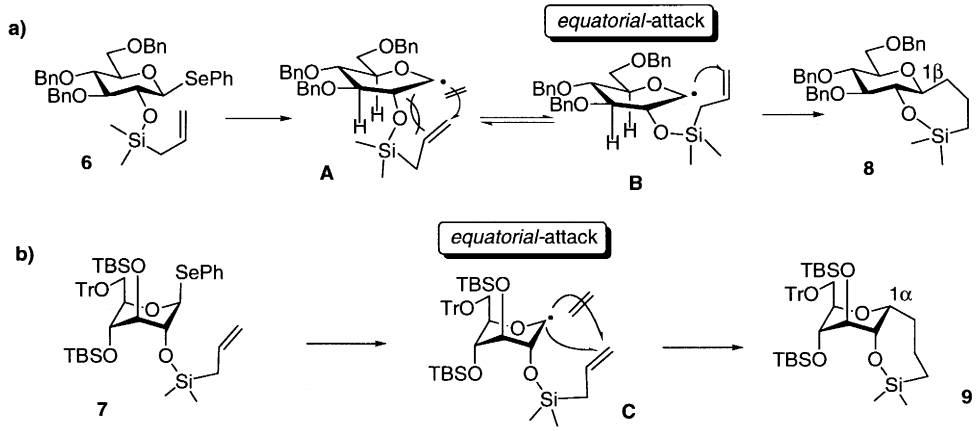


Fig. 1.

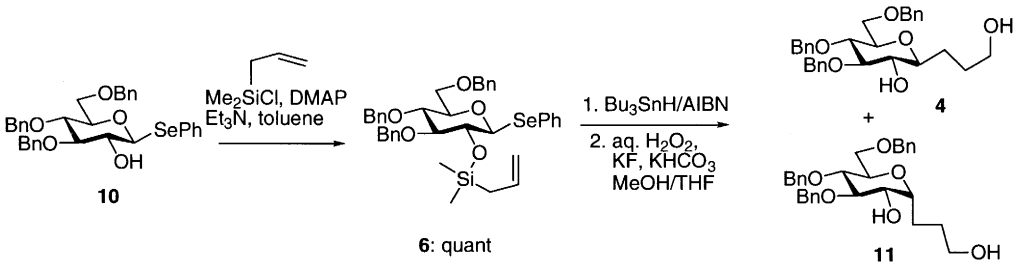
on the conformation of the substrates. Since the approach of the terminal of the tether to the anomeric position from the α-face would not be favored because of significant 1,3-diaxial repulsion (**A** in Scheme 1a), the radical derived from the tri-*O*-benzyl-protected substrate **6** in a boat-like conformation[6] should cyclize selectively via an *equatorial*-attack (**B** in Scheme 1a) to give the 1β-product **8**. On the other hand, the radical reaction of the 3,4-di-*O*-TBS-protected substrate **7**, which would predominantly exist in an unusual $^{1}C_{4}$ conformation due to the significant steric repulsion between the bulky TBS groups,[4,7] would give the α-cyclization product **9** for the following reason. The 1,2-*trans*-cyclization would be impossible sterically because of the *axial* orientation of the 2′-tether, as shown in Scheme 1b. Oxidative treatments[8] of the radical reaction products **8** and **9** would give the corresponding *C*-glucosides having a 3-hydroxypropyl group at the anomeric β- and α-positions, respectively.



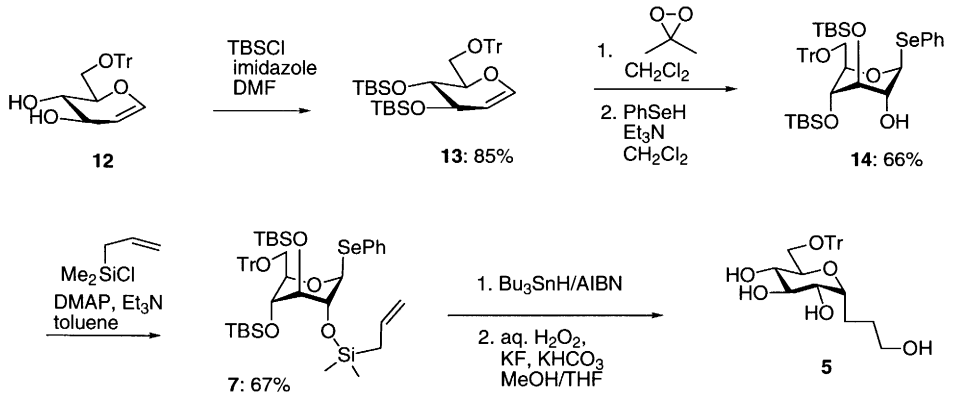
Scheme 1.

Phenyl 3,4,6-tri-*O*-benzyl-1-seleno-β-D-glucose (**10**), which was prepared by a known method,[9] was treated with commercially available allyldimethylsilyl chloride, DMAP, and Et_3N in toluene at room temperature to give the corresponding 2-*O*-allylsilyl ether **6** quantitatively (Scheme 2). The 3,4-*O*-TBS-protected substrate **7** was prepared from the known glycal **12**[10] as shown in Scheme 3. The TBS groups were introduced at the 3,4-*trans*-hydroxyl groups of **12**, and the resulting compound **13** was successively treated with dimethyldioxirane and PhSeH/Et_3N in CH_2Cl_2 to give 1β-phenylselenide **14**. An allyldimethylsilyl tether was then introduced at the 2-hydroxyl group of the phenylselenide **14** to give **7**, the other substrate for the radical reaction.

The conformation of the substrate **7** was investigated by ^{1}H NMR and compared to that of the tri-*O*-benzyl-protected substrate **6** (Fig. 2). While the relatively large coupling constants in the benzyl substrate



Scheme 2.



Scheme 3.

6 suggest that it exits in the usual $^4C_1$-conformation (Fig. 2a), the rather small coupling constants in the TBS-protected compound **7** indicate that it prefers a flipped $^1C_4$-conformation, as expected (Fig. 2b).

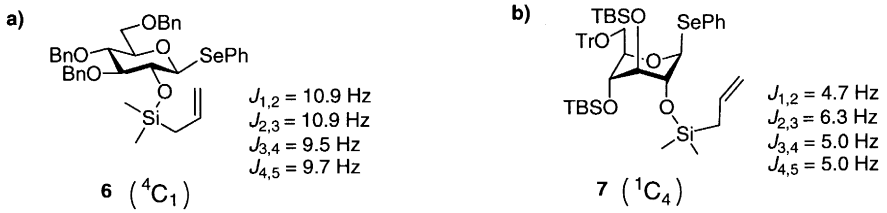


Fig. 2.

The radical reactions of **6** and **7** were performed by adding a mixture of Bu_3SnH and AIBN slowly to a solution of the substrate in benzene (80°C), toluene (110°C), or *t*-butylbenzene (130°C), and the products were isolated after Tamao oxidation.[8] The results are summarized in Table 1. The reaction of **6** (0.005 M) was first carried out in benzene under reflux. The reaction gave selectively the desired β-*C*-glucoside **4** as the major product along with the corresponding α-*C*-glucoside **11**, after Tamao oxidation (entry 1: yield 73%, α:β=1:2.9). When the reaction was performed at 110°C in toluene, both the yield and the stereoselectivity were improved (entry 2: yield 80%, α:β=1:4.1). However, at higher temperatures, the yield decreased (entry 3). Thus the radical reaction and the subsequent Tamao oxidation selectively gave the 1β-*C*-glucoside **4**, as expected.

The reactions with the TBS-protected substrate **7** were next examined. Treatment of **7** under conditions identical to those in entry 1 did not initiate the radical reaction,[11] and the substrate **7** was completely recovered. However, when **7** was reacted with an excess of Bu_3SnH under higher substrate concentration conditions (0.05 M), the reaction gave the desired α-*C*-glucoside **5** as the sole product in 75% yield, after

Table 1
Synthesis of *C*-glucosides by radical reactions with 2-*O*-allylsilyl-tethered substrates[a]

entry	substrate (concn, M)	solvent	temp (°C)	yield	product (ratio)[b]
1	**6** (0.005)	benzene	80	73	**4**, **11** (2.9:1)
2	**6** (0.005)	toluene	110	80	**4**, **11** (4.1:1)
3	**6** (0.005)	*t*-BuPhH	130	62	**4**, **11** (3.1:1)
4	**7** (0.005)	benzene	80		no reaction
5	**7** (0.05)	benzene	80	75	only **5**
6	**7** (0.05)	toluene	110	85	only **5**

[a]To a heated solution of the substrate in benzene, toluene, or *t*-BuPhH, a mixture of Bu_3SnH (entries 1-4, 1.3 equiv; entries 5 and 6, 4.0 equiv) and AIBN (0.6 equiv) in the same solvent was added slowly (entries 1-4, over 4 h; entries 5 and 6, over 1.6 h). [b]Determined by HPLC.

Tamao oxidation (entry 5). Similar treatment of **7** at 110°C in toluene further improved the yield of **5** to 85% (entry 6).

As described, we have developed an efficient method for preparing both 1α- and 1β-*C*-glucosides having a 3-hydroxypropyl group at the anomeric position via the radical cyclization with an allylsilyl tether. We demonstrated that the stereoselectivity of the radical cyclization can be controlled by the conformation of the pyranose ring, which was effectively manipulated by the choice of the hydroxyl protecting groups. The conversion of **4** and **5** into the potential IP_3 ligands **2** and **3** is now under investigation.

Acknowledgements

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