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Synthesis of *C*-glycosides via radical cyclization reactions with a vinylsilyl tether. Control of the reaction course by a change in the conformation of the pyranose ring due to steric repulsion between adjacent bulky protecting groups

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Abstract

A stereoselective method for introducing a C2-unit at the 1α- and 1β-postions of D-glucose and D-mannose, respectively, via a radical cyclization reaction with vinylsilyl group as a temporary connecting tether, was developed. The radical cyclization of D-glucose substrates was effectively facilitated by a change in the conformation of the pyranose ring into a $^1C_4$-form due to steric repulsion between adjacent bulky TBS-protecting groups. © 1999 Elsevier Science Ltd. All rights reserved.

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Due to their unique biological activities, considerable effort has been devoted to the development of useful methods for preparing *C*-glycosides.[1–4] In this communication, we describe a novel procedure for introducing a C2 unit stereoselectively at the 1α-position of D-glucose and the 1β-position of D-mannose via radical cyclization reactions with vinylsilyl groups as a temporary connecting tether.

Recently, we developed a regio- and stereoselective method for introducing a C2-unit at the position adjacent to a hydroxyl group in halohydrins or α-phenylselenoalkanols using an intramolecular radical cyclization reaction with vinylsilyl groups as a radical acceptor tether, as shown in Scheme 1.[5–8] The selective introduction of both 1-hydroxyethyl and 2-hydroxyethyl groups can be achieved via a 5-*exo*-cyclization product **E** or a 6-*endo*-cyclization product **F**, respectively, after ring-cleavage of the cyclization products by Tamao oxidation,[9] as shown in Scheme 1. We also demonstrated that the kinetically favored 5-*exo*-cyclized radical **C**, formed from radical **B**, was trapped when the concentration of Bu_3SnH was high enough to give **E**.[5,6] At lower concentrations of Bu_3SnH and higher reaction temperatures, radical **C** rearranged into the more stable ring-enlarged radical **D**, which was then trapped with Bu_3SnH to give **F**.[5,6]

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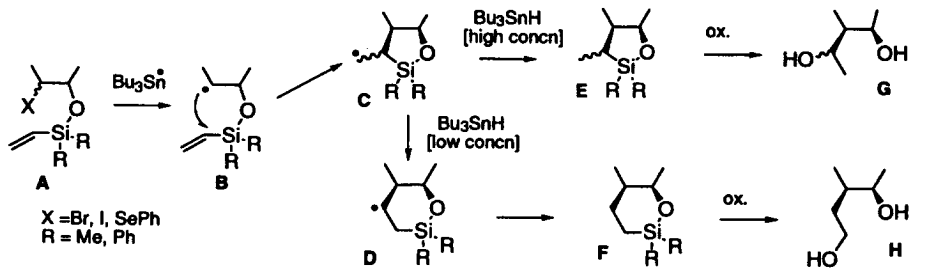
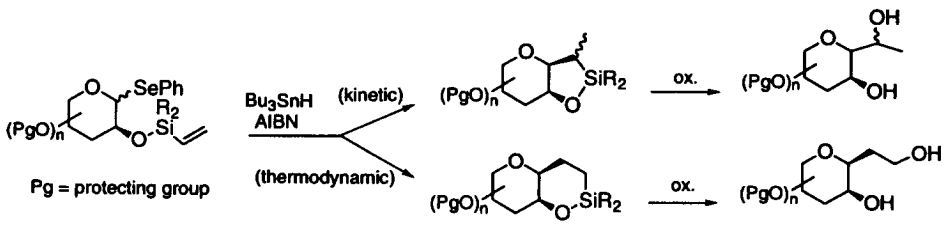


Scheme 1.

We planned to develop an efficient method for preparing *C*-glycosides having a C2-unit at the anomeric position by using this temporary silicon-tethered procedure.[10,11] Scheme 2 shows our synthetic plan, in which phenylselenyl glycosides are chosen as substrates, since they are stable and easy to prepare, and a vinylsilyl tether is introduced at the 2-hydroxyl of the sugars.



Scheme 2.

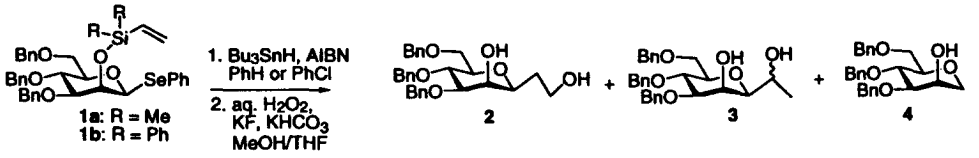
The radical reactions were performed with Bu_3SnH/AIBN in benzene (80°C) or chlorobenzene (130°C), and the products were isolated after Tamao oxidation.[9] The results are summarized in Table 1. First, we examined the reaction with 2-*O*-dimethylvinylsilyl ether of 3,4,6-tri-*O*-benzyl-1-phenylselenyl-β-D-mannose (**1a**, Scheme 3).[12] Radical reactions of **1a** in the presence of 1.3 equiv. of Bu_3SnH and AIBN (0.6 equiv.) in refluxing benzene gave the expected 1-hydroxyethyl β-*C*-mannoside **3**, derived from the corresponding 5-*exo*-cyclized product, as a major product along with 2-hydroxyethyl β-*C*-mannoside **2**, derived from the 6-*endo*-cyclized product, and a directly reduced product **4** (entry 1, yield 90%, **2**:**3**:**4**=6:74:20).[13] Slow addition of Bu_3SnH and AIBN over 1 h to a solution of **1a** prevented the production of **4** and somewhat increased the yield of **2** (entry 2, yield 75%, **2**:**3**:**4**=36:62:2). When the reaction was carried out at 130°C in refluxing chlorobenzene, the regioselectivity was reversed to give **2** as a major product, while the yield was moderate (entry 3, yield 53%, **2**:**3**=62:38). Similarly, the radical reactions of the corresponding 2-*O*-diphenylvinylsilyl ether **1b** gave β-*C*-mannosides **2** and **3** (entries 4–6), while the yield of 2-hydroxyethyl *C*-mannoside **2** was higher under thermodynamic conditions (entry 6, yield 74%, **2**:**3**=86:14) than that in the similar treatment of dimethylvinylsilyl ether **1a** (entry 3).

On the other hand, when the reaction was performed with the 2-*O*-dimethylvinylsilyl ether of 3,4,6-tri-*O*-benzyl-1-phenylselenyl-β-D-glucose (**5**) as a substrate (Scheme 4), the result was undesirable; epimerization at the 5-position and/or elimination of the benzyloxy group at the 4-position gave **8** and/or **9**, and the desired α-*C*-glucosides were not obtained as major products (Table 1, entries 7–10).[13] A deuterium-label experiment with Bu_3SnD was performed under conditions similar to those in entry 7, and the positions and rates of deuterium incorporation in the products based on their ^1H NMR spectra are shown in Fig. 1. These results demonstrated that the methyl radical on *exo*-cyclized intermediate **I** (Fig. 2) abstracted the 5′-hydrogen to generate a stable tertiary radical at the 5-position in the reaction course.[14] The ^1H NMR spectrum of **5** suggested its $^4C_1$-conformation,[15] and accordingly, the methyl

Table 1
Synthesis of *C*-glycosides with vinylsilyl tethers

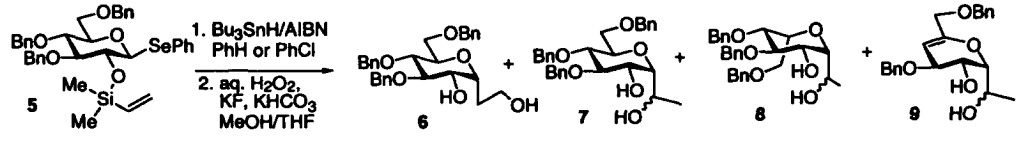
entry	substrate (concn, M)	method[a]	temp (°C)	Yield (%)	product (ratio)[b]
1	**1a** (0.01)	A	80	90	**2, 3, 4** (6:74:20)
2	**1a** (0.002)	B	80	75	**2, 3, 4** (36:62:2)
3	**1a** (0.002)	B	130	53	**2, 3** (62:38)
4	**1b** (0.01)	A	80	67	**2, 3, 4** (22:64:14)
5	**1b** (0.002)	B	80	63	**2, 3** (57:43)
6	**1b** (0.002)	B	130	74	**2, 3** (86:14)
7	**5** (0.01)	A	80	92	**6, 7, 8** (6:57:37)
8	**5** (0.002)	B	80	65	**6, 7, 8, 9** (31:20:40:9)
9	**5** (0.002)	B	130	45	**6, 9** (20:80)
10	**14a** (0.01)	A	80	85	**16, 17** (6:94)
11	**14a** (0.002)	B	130	50	**16, 17** (74:26)
12	**14b** (0.01)	A	80	87	**16, 17** (16:84)
13	**14b** (0.002)	B	130	63	**16, 17** (87:13)
14	**15** (0.01)	A	80	85	**16, 17** (11:89)
15	**15** (0.002)	B	130	60	**16, 17** (77:23)

[a] A: A mixture of the substrate and Bu_3SnH (1.3 equiv) and AIBN (0.6 equiv) in benzene was heated under reflux for 20 min. B: To a refluxing solution of the substrate in benzene (at 80 °C) or chlorobenzene (at 130 °C), a mixture of Bu_3SnH (1.3 equiv) and AIBN (0.6 equiv) in benzene or chlorobenzene was added slowly over 1 h. [b]Determined by HPLC.



Scheme 3.

radical on the *exo*-cyclized radical intermediate **I** may be located very close to the 5-position, since the intermediate would adopt a conformation similar to that of **5**.



Scheme 4.

Recently, Suzuki reported that introducing significantly bulky protecting groups at 3,4-*trans*-hydroxyls of pyranoses causes a flip of their conformation leading to an unusual $^1C_4$-form in which the bulky substituents are in axial positions due to the mutual steric repulsion.[16,17] Therefore, we selected 3,4,6-tris-*O*-TBS-D-glucose derivatives **14** and **15** as alternative substrates which might adopt a $^1C_4$-conformation because of the steric effect of bulky TBS groups. If this expectation was met, the *exo*-cyclized intermediate **II** derived from **14** or **15** would also prefer a $^1C_4$-conformation to avoid undesired hydrogen abstraction, as shown in Fig. 2. The substrates **14a**, **14b**, and **15** were prepared from a known glycal, **10**[18,19] as shown in Scheme 5. These 3,4-bis-*O*-TBS substrates were investigated by ^1H NMR, which

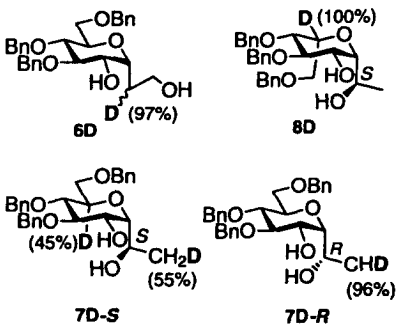


Figure 1.

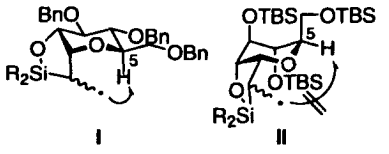
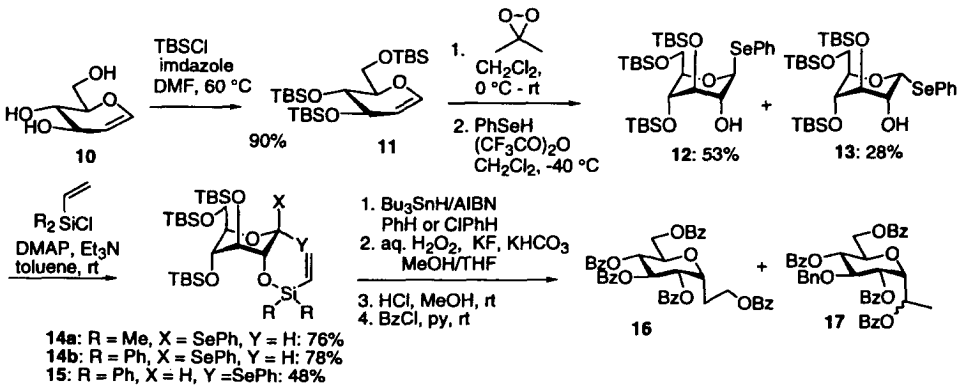


Figure 2.

suggested that they had a $^1C_4$-conformation, as we expected.[20] Radical reactions of **14a**, **14b**, and **15** were carried out under kinetic [treatment in the presence of Bu_3SnH (1.3 equiv.)/AIBN (0.6 equiv.) at 80°C] or thermodynamic [slow addition of Bu_3SnH (1.3 equiv.)/AIBN (0.6 equiv.) over 1 h at 130°C] conditions, and the products were obtained as the corresponding pentabenzoates (Scheme 5). As a result, this conformation-flip strategy effectively improved the yields of the desired *C*-glucosides, and the products via the 5-proton abstraction reaction were not detected at all. Thus, both 2-hydroxyethyl *C*-glucoside **16** and 1-hydroxyethyl *C*-glucoside **17** were obtained selectively under thermodynamic (entries 11, 13, and 15) and kinetic (entries 10, 12, and 14) conditions, respectively.[13] In these reactions, α-selenide **14b** and β-selenide **15** gave similar results.



Scheme 5.

In conclusion, we have developed a stereoselective method for introducing a C2-unit at the 1α- and 1β-postions of D-glucose and D-mannose, respectively, via a radical cyclization reaction with a temporary vinylsilyl connecting tether. We also found that the reaction course of the radical cyclization of glucose substrates was effectively controlled by a change in the conformation of the pyranose ring due to steric repulsion between the adjacent bulky protecting groups at the 3- and 4-positions.

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12. The 2-*O*-vinylsilyl ethers **1a**, **1b**, and **5** were prepared in high yields by treating 3,4,6-tri-*O*-benzyl-1-phenylselenyl-β-D-mannose or -glucose with commercially available dimethyl- or diphenylvinylsilyl chloride (4.0 equiv.), DMAP (0.1 equiv.), and Et_3N (4.0 equiv.) in toluene at room temperature.
13. Each of the compounds was purified by C18 HPLC.
14. The results on **7D**-*S* and **7D**-*R*, and **8D** suggested that 5-hydrogen abstraction proceeded mainly via the 1′*S*-*exo*-cyclized intermediate. The 1′-stereochemistries of (1′*S*)-**7** and (1′*R*)-**7** were confirmed by NOE experiments, after **7** (a diastereomeric mixture at the 1′-position) was converted into the corresponding 2,1′-*O*-isopropylidene derivatives where the 1′*S*-and 1′*R*-isomers were successfully separated.
15. Coupling constants (Hz) between ring-protons of **5** were as follows: $J_{1,2}$=9.8, $J_{2,3}$=8.4, $J_{3,4}$=8.8, $J_{4,5}$=9.4, which suggested that all of the ring protons were in axial positions.
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20. Coupling constants (Hz) between ring-protons of **14a** were as follows: $J_{1,2}$=5.1, $J_{2,3}$=ca. 0, $J_{3,4}$=ca. 0, $J_{4,5}$=ca. 0, which suggested that H-2, -3, -4, and -5 were in equatorial positions.