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Efficient synthesis of β-*C*-glucosides via radical cyclization with a silicon tether based on the conformational restriction strategy

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Abstract—An efficient method for preparing β-*C*-glucosides using radical cyclization with a temporary connecting silicon tether was developed. In this reaction, conformational restriction of the substrates to the unusual $^1C_4$-form is essential for the cyclization to occur.

C-Glycosides are stable mimics for natural *O*-glycosides possessing biological activity.[1] During our studies on *C*-glycosidic ligands of *myo*-inositol 1,4,5-trisphosphate (IP_3) receptors,[2] we newly designed the β-*C*-glucoside trisphosphates **1** and **2** (Fig. 1) as stable IP_3 mimics. Owing to the six-membered chair-conformation of these compounds, the 3,4-*trans*-bisphosphate on D-glucose backbone of **1** and **2** can be superimposed with the 4,5-*trans*-bisphosphate of IP_3.

Although numerous methods exist for the preparation of *C*-glycosides, the synthesis of β-*C*-glycosides has proved to be considerably more difficult than the synthesis of their α-counterparts.[1,3d] The use of radical reactions is an efficient process for constructing *C*-glycosidic bonds, and stereoselective intramolecular and intermolecular radical *C*-glycosidation reactions have been developed.[1,2b,c,3b,c,4] Stork et al. reported a facile synthesis of a β-*C*-glucoside via the stereoselective radical cyclization using a phenyl l-seleno-β-D-glucose derivative having a phenylethynylsilyl group as a radical acceptor tether at the 6-hydroxyl.[4] As shown in Scheme 1, heating the substrate with Bu_3SnH and AIBN in benzene, followed by treatment with TBAF, gave the 2-phenylvinyl β-*C*-glucoside in 54% yield. They described the radical cyclization as proceeding via a conformationally flipped intermediate that assumes the $^1C_4$-form (Scheme 1).[4] In this conformation, the tethered hydroxymethyl moiety adopts an axial orientation, placing the radical-accepting sp carbon of the ethynyl moiety close to the anomeric radical, thereby allowing the cyclization to occur.

Based on these results, we speculated that effective introduction of a carbon-unit at the anomeric β-position could be realized via radical cyclizations with substrates **I** conformationally restricted to the unusual $^1C_4$-form.

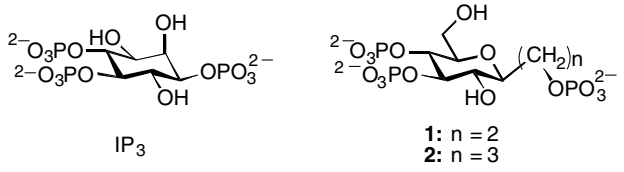
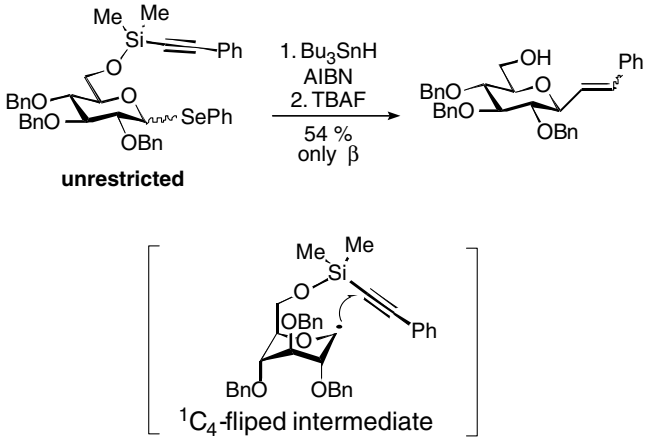


Figure 1. IP_3 and newly designed β-*C*-glucosidic IP_3 mimics.



Scheme 1.

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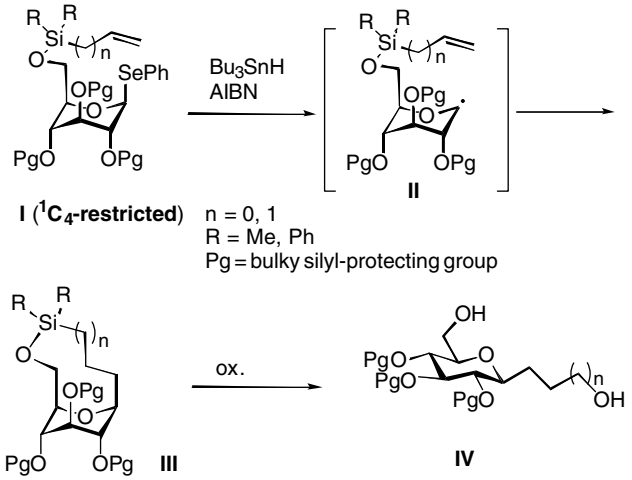


Scheme 2.

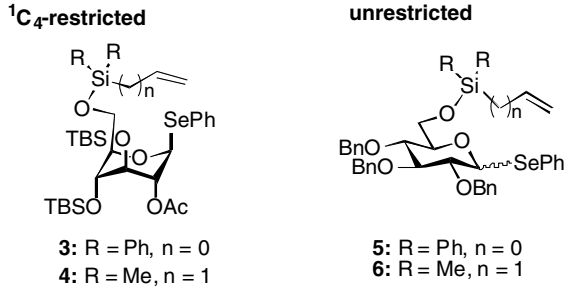


Figure 2. Conformationally restricted and unrestricted substrates for the radical cyclization.

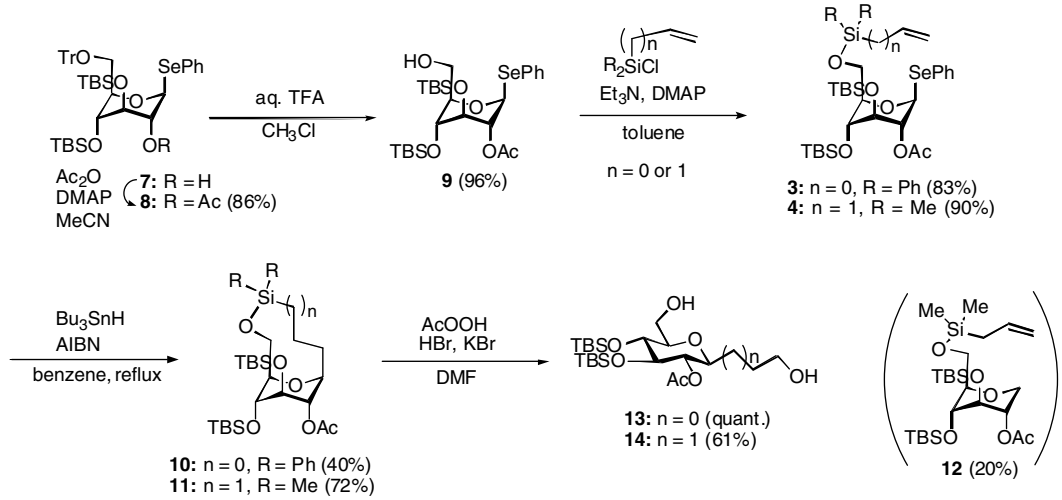
As shown in Scheme 2, the radical reaction using the $^1C_4$-restricted substrate **I** was expected to form stereoselectively the desired β-cyclization product **III**, via the $^1C_4$-chair-like anomeric radical intermediate **II**, in which the *cis*-cyclization would effectively occur without conformational change because of the *axial* orientation of the 6′-hydroxylmethyl moiety with the tether. Oxidative cleavage of the C–Si bond would produce the desired β-*C*-glucoside **IV**. Thus, we designed the radical reaction substrates **3** and **4** with a 6-*O*-vinylsilyl[5] or a 6-*O*-allylsilyl[6] group as the radical-accepting tether (Fig. 2), the conformation of which can be restricted by significantly bulky silyl-protecting groups at the secondary hydroxyl groups.[3,7]

The synthesis of the substrates **3** and **4** is shown in Scheme 3. The 2-hydroxyl of the phenyl 3,4-bis-TBS-6-*O*-trityl-l-seleno-β-D-glucose (**7**)[2c] was acetylated, and the 6-*O*-trityl group of the product **8** was selectively removed with aqueous TFA to give **9**. Treatment of **9** with vinyldiphenylchlorosilane/DMAP/Et_3N in toluene at room temperature gave the 6-*O*-vinylsilyl ether **3**. Similarly an allyldimethylsilyl group was introduced at the 6-hydroxyl with allyldimethylchlorosilane to give the other substrate **4**.

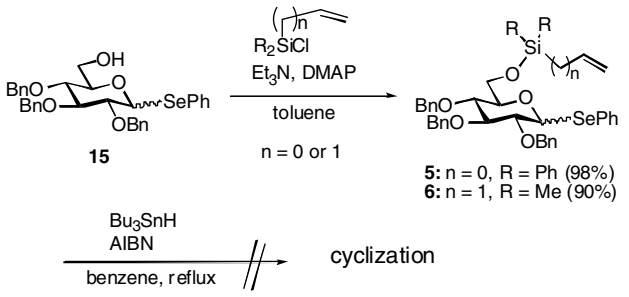
The conformationally unrestricted substrates, that is, 6-*O*-vinyldiphenylsilyl and 6-*O*-allyldimethylsilyl ethers **5** and **6** of tri-*O*-benzyl-protected l-phenylseleno-β-D-glucose, were also prepared from phenyl 2,3,4-tri-*O*-benzyl-l-seleno-β-D-glucose (**15**),[4] as shown in Scheme 4, in order to clarify whether the conformational restriction of the substrates to the $^1C_4$-form actually facilitated the β-selective radical cyclization.

The unrestricted substrates **5** and **6** had large coupling constants (ca. 9 Hz) between the ring protons in ^{1}H NMR,[8] showing their preference for the usual $^4C_1$-chair-like conformation. On the other hand, the considerably smaller coupling constants between the ring protons in the 3,4-*O*-silyl-protected substrates **3** and **4**[8] suggested that these preferred the flipped $^1C_4$-like conformation.

These radical reactions of the $^1C_4$-restricted substrates **3** and **4** as well as the unrestricted substrates **5** and **6** were performed by slow addition of a mixture of Bu_3SnH (1.2 equiv) and AIBN (0.6 equiv) to a heated solution of the substrate (5 mM) in benzene (80 °C) (Schemes 3 and 4). The reaction was carried out first with the



Scheme 3.



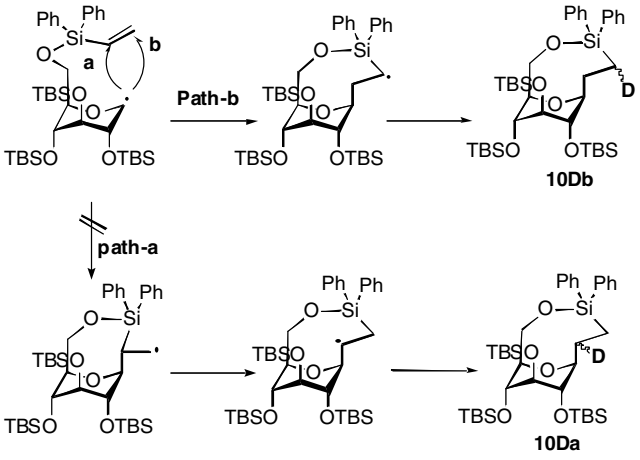
Scheme 4.

$^1C_4$-restricted vinylsilyl ether **3**, and afforded the desired β-*endo*-cyclization product **10** in 40% yield. When the $^1C_4$-restricted allylsilyl ether **4** was subjected to the reaction under the same conditions, the *endo*-cyclization effectively occurred to give the desired β-product **11** in 72% yield along with the anomeric reduction product **12** in 20% yield.[9] On the other hand, in the treatment of either of the conformationally unrestricted substrates **5** or **6** under similar Bu_3SnH/AIBN conditions, many spots were observed on TLC, and none of the cyclization products were obtained (Scheme 4).

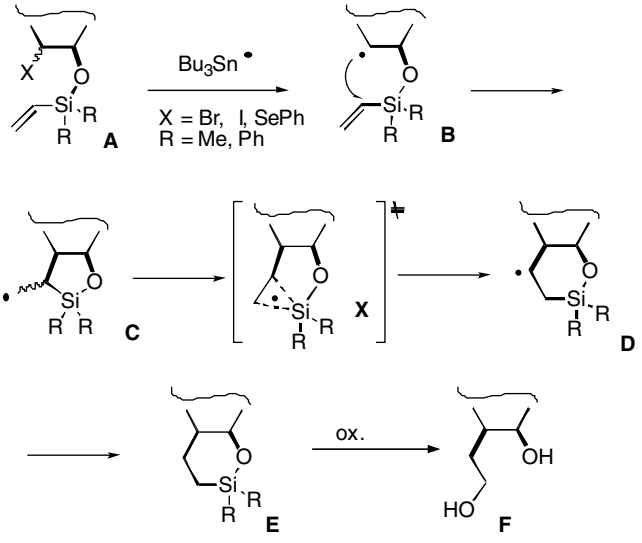
These results show that the conformational restriction strategy works effectively in radical cyclization. It is worth noting that the reaction of the allylsilyl ether **4** produced the unusual 9-*endo*-cyclization product **11** in good yield. In the case of the vinylsilyl ether **3**, although the yield was not high, the $^1C_4$-conformational restriction of the substrate allowed the formation of the unusual 8-*endo*-cyclization product **10**.

We previously developed a regio- and stereoselective method for introducing a C2-substituent at the β-position of a hydroxyl in halohydrins or α-phenylselenoalkanol substrate **A** using an intramolecular radical cyclization with a vinylsilyl group as a temporary connecting radical acceptor tether (Scheme 5).[5] The selective introduction of a 2-hydroxyethyl group can be achieved via the 6-*endo*-type cyclization product **E**, after oxidative ring-cleavage by treating the cyclization product under Tamao oxidation conditions.[5] During these studies, we showed that the kinetically favored 5-*exo*-cyclized radical **C**, initially formed from radical **B**, rearranged to the more stable ring-enlarged 4-oxa-3-silacyclohexyl radical **D** via a pentavalent-like silicon radical transition state **X**, which was then trapped with Bu_3SnH to give **E**.[5c]

We were interested in the reaction pathway forming the 8-*endo*-cyclization product **10**, which can be formed, as shown in Scheme 6, either via the ring-enlarged rearrangement (path a), analogous to the previous case (Scheme 5), or via the direct 8-*endo*-cyclization (path b).[9] Thus, a deuterium-labeling experiment of the substrate **3** with Bu_3SnD instead of Bu_3SnH was carried out. The radical cyclization product was identified by ^1H and ^2H NMR analyses not as **10Da** but as **10Db**,



Scheme 6.



Scheme 5.

in which only the protons of the methylene adjacent to the silicon were replaced exclusively by deuterium, demonstrating that the direct 8-*endo*-cyclization (path b) had occurred in this case.[10]

The eight- or nine-membered ring-opening via the oxidative Si–C bond fission was next examined. The desired Si–C bond fission was achieved without removing the silyl-protecting groups by treatment of **10** or **11** with AcOOH/HBr/KBr in DMF,[11] where the β-*C*-glucosides **13** and **14** were obtained quantitatively and in 61% yield, respectively.

As described above, we have developed an efficient method for preparing β-*C*-glucosides via a radical cyclization based on the $^1C_4$-conformational restriction strategy.[12] The reaction can be effectively employed as the key step in the synthesis of the *C*-glucoside trisphosphates **1** and **2**, designed as potential IP_3 receptor ligands, which is now under investigation.

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8. Compound **3**, $J_{2,3} = 4.2$ Hz; **4**, $J_{2,3} = 2.0$ Hz, $J_{3,4} =$ ca. 0 Hz; **5**, $J_{2,3} = J_{3,4} = J_{4,5} = 9.4$ Hz; **6**, $J_{2,3} = J_{3,4} = J_{4,5} =$ 8.7 Hz.
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