Synthesis of 3,7-Anhydro-D-*glycero*-D-*ido*-octitol 1,5,6-Trisphosphate as an IP_3 Receptor Ligand Using a Radical Cyclization Reaction with a Vinylsilyl Tether as the Key Step. Conformational Restriction Strategy Using Steric Repulsion between Adjacent Bulky Protecting Groups on a Pyranose Ring

Satoshi Shuto,* Yumi Yahiro, Satoshi Ichikawa, and Akira Matsuda

Graduate School of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060-0812, Japan

shu@pharm.hokudai.ac.jp

Received February 18, 2000

3,7-Anhydro-D-*glycero*-D-*ido*-octitol 1,5,6-trisphosphate (**5**) was designed as a novel IP_3-receptor ligand having a *C*-glycosidic structure and was synthesized via a radical cyclization reaction with a temporary connecting vinylsilyl tether as the key step. The phenyl 2-*O*-dimethylvinylsilyl-3,4,6-tri-*O*-benzyl-1-seleno-β-D-glucopyranoside (**7**), in the usual $^4C_1$-conformation, was successively treated with Bu_3SnH/AIBN and under Tamao oxidation conditions to give a mixture of five *C*-glycosidic products. On the other hand, similar successive treatment of the corresponding 3,4-di-*O*-TBS-protected substrates **13** and **24**, which were in an unusual $^1C_4$-conformaion due to the steric repulsion between the bulky silyl protecting groups, gave the desired 1α-*C*-glycosides **18** and **25**, respectively, as the major products. Thus, the course of the radical cyclization was effectively controlled by a change in the conformation of the pyranose ring into a $^1C_4$-form due to steric repulsion between the adjacent bulky TBS-protecting groups at the 3- and 4-hydroxyl groups. From **25**, the target **5** was synthesized via phosphorylation of the hydroxyls by the phosphoramidite method. The *C*-glycoside trisphosphate **5** has significant binding affinity for IP_3 receptor of calf cerebella.

Introduction

D-*Myo*-inositol 1,4,5-trisphosphate (IP_3, **1**),[1] an intracellular Ca^{2+}-mobilizing second messenger, is of great interest because of its significant biological importance.[2] Accordingly, analogues of IP_3 have been synthesized extensively to develop specific ligands for the receptors, which are very useful for proving the mechanism of IP_3-mediated Ca^{2+} signaling pathways.[3] However, none of these analogues has surpassed IP_3 itself either in binding affinity for the IP_3 receptor or Ca^{2+}-mobilizing activity.[3]

Recently, Takahashi and co-workers isolated adenophostin A (**2**) and B (**3**) from *Penicillium brevicompactum* and found them to be very strong IP_3 receptor ligands. Compounds **2** and **3** are 10−100 times more potent than IP_3 with regard to both their affinity for the IP_3 receptor and their Ca^{2+}-mobilizing ability in cells.[4] These interesting biological and structural features have prompted several groups including ours to perform synthetic studies of novel IP_3 receptor ligands based on the structure of adenophostins.[5,6] For instance, two groups[6a,b,g] independently designed and synthesized 2-hydroxyethyl α-D-glucopyranoside 3,4,2′-trisphosphate (**4**) as a simplified analogue of the adenophostins and showed that it was an agonist of the IP_3 receptor. These studies also indicated that the α-D-glucopyranose structure is a good bioisostere of the *myo*-inositol backbone of IP_3.

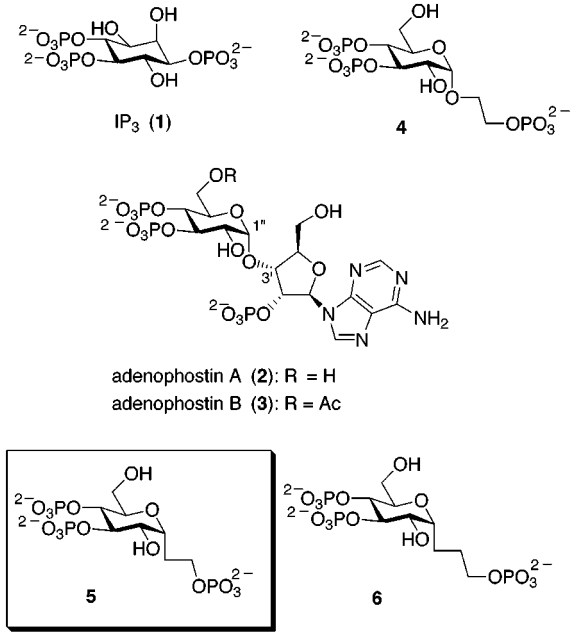


Figure 1.

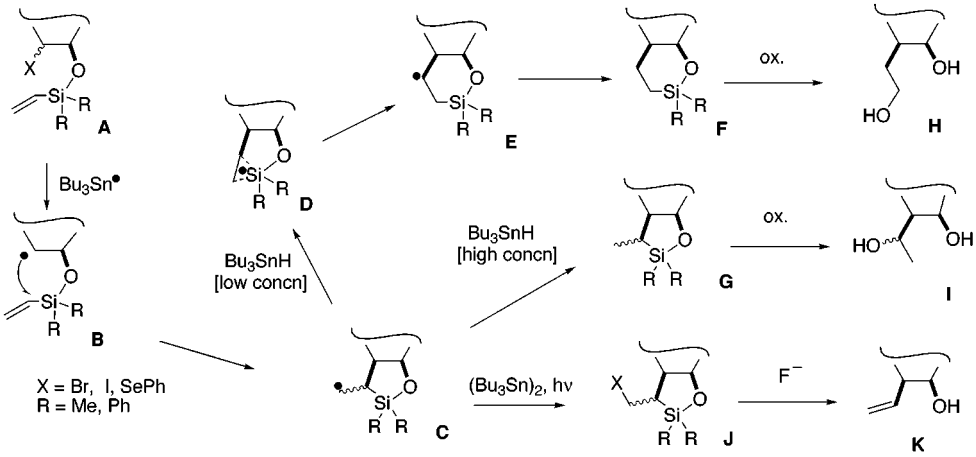
On the basis of these findings, we became interested in the corresponding *C*-glycosidic analogues having the α-D-glucopyranoside structure as potential IP_3 receptor

* Corresponding author: Tel: 81-11-706-3229; Fax: 81-11-706-4980.

(1) Berridge, M. J. *Nature (London)* **1993**, *361*, 315−325.
(2) Wilcox, R. A.; Primrose, W. U.; Nahorski, S. R.; Challiss, R. A. J. *Trends Pharmacol. Sci.* **1998**, *19*, 467−475.
(3) Potter, B. V. L.; Lampe, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1933−1972, and references sited therein.
(4) (a) Takahashi, M.; Kagasaki, T.; Hosoya, T.; Takahashi, S. *J. Antibiot.* **1993**, *46*, 1643−1647. (b) Takahashi, S.; Kinoshita, T.; Takahashi, M. *J. Antibiot.* **1994**, *47*, 95−100. (c) Takahashi, M.; Tanzawa, K.; Takahashi, S. *J. Biol. Chem.* **1994**, *269*, 369−372. (d) Hirota, J.; Michikawa, T.; Miyawaki, A.; Takahashi, M.; Tanzawa, K.; Okura, I.; Furuichi, T.; Mikoshiba, K. *FEBS Lett.* **1995**, *368*, 248−252.

10.1021/jo0002339 CCC: $19.00
Published on Web 08/10/2000

Scheme 1

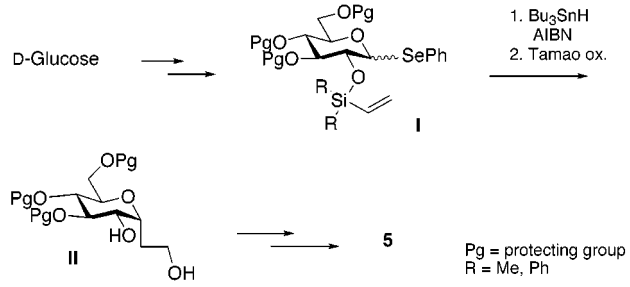


ligands. Since *C*-glycosides can be a biologically stable mimic of the corresponding *O*-glycosides,[7] we designed the α-*C*-glycoside trisphosphates **5** and **6** as novel IP_3 receptor ligands.

It has been recognized that the three-dimensional locations of the phosphate groups of IP_3 receptor ligands are critical points for their biological activity.[3,5] The conformation around the glycosidic linkages in carbohydrates, such as the adenophostins and their analogues, which is known to be affected significantly by the anomeric effect of the sugar-ring oxygen, is an important determinant in the three-dimensional structure of these molecules.[8] Therefore, we were interested in investigating the biological activity and the conformation of **6** with the biological activity and the conformation of the corresponding *O*-glycoside **4**. We thought that the data from this investigation might indicate the role of the glycosidic oxygen in the biological activity of these compounds.

Although the *O*-glycoside trisphosphate **4** is an agonist of the IP_3 receptor, its potency is ∼10-fold lower than IP_3.

Scheme 2



We hypothesized that the lower affinity of **4** for the receptor compared to that of IP_3 itself may be due to the length of the side-chain, which may be too long to allow the third phosphate to achieve an efficient positioning for binding to the receptor. Therefore, to test this hypothesis, we designed the one-carbon-reduced analogue **5**.[9] In this report, we describe the synthesis of the α-*C*-glycoside trisphosphate **5** using a radical reaction with a temporary connecting vinylsilyl tether as the key *C*-glycosidation step. During our synthetic study, we found that the reaction course of the radical cyclization of the D-glucose substrates was effectively controlled by a change in the conformation of the pyranose ring to a $^1C_4$-form because of the steric repulsion between the adjacent bulky TBS-protecting groups at the 3- and 4-hydroxyl groups.[10]

Results and Discussion

Synthetic Plan. In the synthesis of the target compound **5**, formation of the *C*-glycosidic linkage with the desired 1α-configuration is considered the key step. Because of the unique biological activities of *C*-glycosides, considerable effort has been devoted to developing practical methods for their preparation.[7] 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.[7]

Recently, we developed a regio- and stereoselective method for introducing three kinds of C2-substituents, such as 1-hydroxyethyl, 2-hydroxyethyl, and vinyl groups

(5) Studies on analogues of adenophostin A by us: (a) Tatani, K.; Shuto, S.; Ueno, Y.; Matsuda, A. *Tetrahedron Lett.* **1998**, *39*, 5065−5068. (b) Shuto, S.; Tatani, K.; Ueno, Y.; Matsuda, A. *J. Org. Chem.* **1998**, *63*, 8815−8824. (c) Kashiwayanagi, M.; Tatani, K.; Shuto, S.; Matsuda, A. *Eur. J. Neurosci.* **2000**, *12*, 606−612. (d) Abe, H.; Shuto, S.; Matsuda, A. *Tetrahedron Lett.* **2000**, *41*, 2391−2394. (e) Shuto, S.; Terauchi, M.; Yahiro, Y.; Abe, H.; Ichikawa, S.; Matsuda, A *Tetrahedron Lett.*, **2000**, *41*, 4151−4155. (f) Abe, H.; Shuto, S.; Matsuda, A. *J. Org. Chem.* **2000**, *65*, 4315−4325.

(6) Studies on the analogues of adenophostin A by others: (a) Jenkins, D. J.; Marwood, R. D.; Potter, B. V. L. *Carbohydr. Res.* **1996**, *287*, 169−182. (b) Marchant, J. S.; Beecroft, M. D.; Riley, A. M.; Jenkins, D. J.; Marwood, R. D.; Taylor, C. W.; Potter, B. V. L. *Biochemistry* **1997**, *36*, 12780−12790. (c) Murphy, C. T.; Riley, A. M.; Lindley, C. J.; Jenkins, D. J.; Westwick, J.; Potter, B. V. L. *Mol. Pharmacol.* **1997**, *52*, 741−748. (d) Marwood, R. D.; Riley, A. M.; Vanessa, C.; Taylor, C. W.; Potter, B. V. L. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 453−459. (e) Beecroft, M. D.; Marchant, J. S.; Riley, A. M.; van Straten, N. C. R.; van der Marel, G. A.; van Boom, J. H; Potter, B. V. L.; Taylor, C. W. *Mol. Pharmacol.* **1999**, *55*, 109−116. (f) Marwood, R. D.; Shuto, S.; Jenkins, D. J.; Potter, B. V. L. *Chem. Commun.* **2000**, 219−220. (g) Wilcox, R. A.; Erneux, C.; Primrose, W. U.; Gigg, R.; Nahorski, S. R. *Mol. Pharmacol.* **1995**, *47*, 1204−1211. (h) van Straten, N. C. R.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron* **1997**, *53*, 6523−6538. (i) van Straten, N. C. R.; Kriek, N. M. A. J.; Cziria, Z. A. C.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron* **1997**, *53*, 6539−6554. (j) Hotoda, H.; Murayama, K.; Miyamoto, S.; Iwata, Y.; Takahashi, M.; Kawase, Y.; Tanzawa, K.; Kaneko, M. *Biochemistry* **1999**, *38*, 9234−9241.

(7) (a) Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545−8599. (b) Jaramillo, C.; Knapp S. *Synthesis* **1994**, 1−20. (c) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Oxford: Pergamon Press: 1995. (d) Postema, M. H. D. *C-Glycoside Synthesis*; CRC Press: Boca Raton, 1995.

(8) (a) Juaristi, E.; Cuevas, G. *Tetrahedron* **1992**, *48*, 5019−5087. (b) Chapleur, Y. Eds.; *Carbohydrate Mimics*; Wiley-VCH: Weinheim, 1998.

(9) Synthesis of the corresponding *O*-glycoside of **5** may be difficult, since the compound would be rather unstable due to the phosporyloxymethyloxy ($-OCH_2OPO_3^{2-}$) substituent at the anomeric position.

(10) A part of this study has been described in a communication: Yahiro, Y.; Ichikawa, S.; Shuto, S.; Matsuda, A. *Tetrahedron Lett.* **1999**, *40*, 5527−5531.

Scheme 3

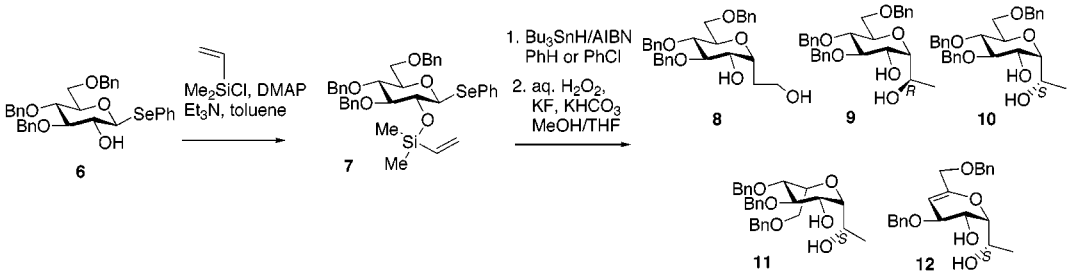


Table 1. Synthesis of *C*-glycosides by the Radical Reactions with 2-*O*-Vinylsilyl-Tethered Substrates

entry	substrate (concn, M)	method[a]	solvent	temp (°C)	yield	product (ratio)[b]
1	**7** (0.01)	A	benzene	80	92	**8**, **9**, **10**, **11** (6:35:22:37)
2	**7** (0.002)	B	benzene	80	92	**8**, **9**, **10**, **11**, **12** (31:20:12:28:9)
3	**7** (0.002)	B	ClPhH	130	45	**8**, **12** (20:80)
4	**13a** (0.01)	A	benzene	80	85	**18**, **19**, **20** (6:49:45)
5	**13a** (0.002)	B	ClPhH	130	50	**18**, **19**, **20** (74:15:11)
6	**13b** (0.002)	B	ClPhH	130	63	**18**, **19**, **20** (87:6:7)
7	**13c** (0.002)	B	ClPhH	130	60	**18**, **19**, **20** (77:8:15)

[a] A: A mixture of the substrate, 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 or chlorobenzene (ClPhH) was added slowly over 1 h a mixture of Bu_3SnH (1.3 equiv) and AIBN (0.6 equiv) in the same solvent. [b] Determined by HPLC.

at the β-position of a hydroxyl group in halohydrins or in α-phenylselenoalkanols **A** using an intramolecular radical cyclization reaction with a dimethyl- or a diphenylvinylsilyl group as a temporary connecting radical-acceptor tether (Scheme 1).[11] Thus, the selective introduction of both 1-hydroxyethyl and 2-hydroxyethyl groups can be achieved, depending on the concentration of Bu_3SnH in the reaction system, via a 5-*exo*-cyclization intermediate **G** or a 6-*endo*-cyclization intermediate **F**, respectively, after oxidative ring-cleavage by treating the cyclization products under Tamao oxidation conditions,[12] as shown in Scheme 1.[11a,b] A vinyl group can also be introduced by photoirradiation of the vinylsilyl ether **A** in the presence of $(Bu_3Sn)_2$ followed by treatment of the resulting atom-transfer 5-*exo*-cyclization product **J** with fluoride ion.[11e] The results of our investigation of the radical cyclization mechanism[11a,b,f,g] suggested 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 **G**. At lower concentrations of Bu_3SnH and higher reaction temperatures, the radical **C** rearranged into the more stable ring-enlarged 4-oxa-3-silacyclohexyl radical **E** via a pentavalent-like silicon radical transition state **D**, which was then trapped with Bu_3SnH to give **F**.[11g]

We planned to develop a novel procedure for introducing a C2 unit stereoselectively at the 1α-position of D-glucose via this radical cyclization reaction with a vinylsilyl group as a temporary connecting tether and then to apply this procedure to the synthesis of the target *C*-glycoside **5**. Scheme 2 shows our synthetic plan. We chose the phenyl 1-seleno-D-glucopyranosides **I** with a vinylsilyl tether at the 2-hydroxyl as the substrates for the radical reaction because they are stable and easy to prepare. The radical reaction under thermodynamic conditions and subsequent Tamao oxidation would give the desired *C*-glycosides **II**, which could then be converted into the target trisphosphate **5** via introduction of the three phosphate groups using the phosphoramidite method.

Radical Reactions with 2-*O*-Vinylsilyl Ethers of Phenyl 3,4,6-Tri-*O*-benzyl-1-seleno-β-D-glucose as the Substrate. First, the radical reaction was investigated with the 2-*O*-dimethylvinylsilyl ether of 3,4,6-tri-*O*-benzyl-protected phenyl l-seleno-β-D-glucose (**7**) as the substrate. Phenyl 3,4,6-tri-*O*-benzyl-1-seleno-β-D-glucose (**6**), prepared by the known method,[13] was treated with commercially available dimethylvinylchlorosilane, DMAP, and Et_3N in toluene at room temperature to give the corresponding 2-*O*-silyl ether **7**, the substrate for the radical reaction, in high yield (Scheme 3).

The radical reactions were performed with Bu_3SnH (1.3 equiv)/AIBN (0.6 equiv) in benzene (80 °C) or chlorobenzene (130 °C), and the products were obtained after Tamao oxidation. The results are summarized in Table 1. A mixture of **7**, Bu_3SnH, and AIBN was heated in benzene under reflux (kinetic conditions). The reaction gave a mixture of four α-*C*-glycosides, i.e., the desired 2-hydroxyethyl derivative **8** via the 6-*endo*-cyclization product, the 1-hydroxyethyl derivatives **9** and **10** via the corresponding 5-*exo* cyclization products, and 5-epimerized 1-hydroxyethyl derivative **11** in a ratio of 6:35:22:37 (entry 1). When a mixture of Bu_3SnH and AIBN in benzene was added slowly to a solution of **7** in refluxing benzene (thermodynamic conditions), the result was a mixture of **8**, **9**, **10**, **11**, and compound **12** in which the 4-benzyloxy group had been eliminated (entry 2). A similar reaction under thermodynamic conditions at 130 °C with chlorobenzene as a solvent likewise proved unsuccessful and gave **12** as the major product (entry 3).

(11) (a) Shuto, S.; Kanazaki, M.; Ichikawa, S.; Matsuda, A. *J. Org. Chem.* **1997**, *62*, 5676−5677. (b) Shuto, S.; Kanazaki, M.; Ichikawa, S.; Minakawa, N.; Matsuda, A. *J. Org. Chem.* **1998**, *63*, 746−754. (c) Ueno, Y.; Nagasawa, Y.; Sugimoto, I.; Kojima, N.; Kanazaki, M.; Shuto, S.; Matsuda, A. *J. Org. Chem.* **1998**, *63*, 1660−1667. (d) Sugimoto, I.; Shuto, S.; Mori, S.; Shigeta, S.; Matsuda, A. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 385−388. (e) Sugimoto, I.; Shuto, S.; Matsuda, A. *J. Org. Chem.* **1999**, *64*, 7153−7157. (f) Sugimoto, I.; Shuto, S.; Matsuda, A. *Synlett* **1999**, 1766−1768. (g) Shuto, S.; Sugimoto, I.; Abe, H.; Matsuda, A. *J. Am. Chem. Soc.* **2000**, *122*, 1343−1351. (h) Kanazaki, M.; Ueno, Y.; Shuto, S.; Matsuda, A. *J. Am. Chem. Soc.* **2000**, *122*, 2422−2432.

(12) Tamao, K.; Ishida, N.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 2120−2122.

(13) Synthesis of *C*-glycosides via radical cyclizations with a (2-phenylethynyl)silyl tether has been reported: Stork, G.; Suh, H. S.; Kim, G. *J. Am. Chem. Soc.* **1991**, *113*, 7054−7055.

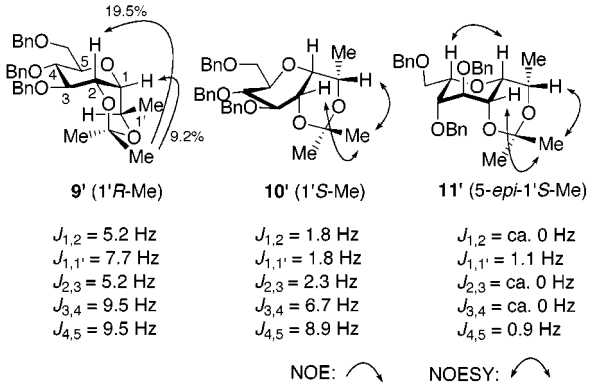


Figure 2.

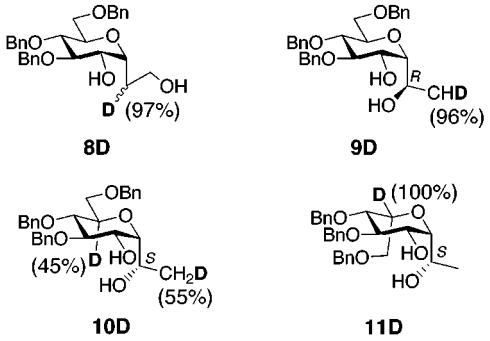


Figure 3.

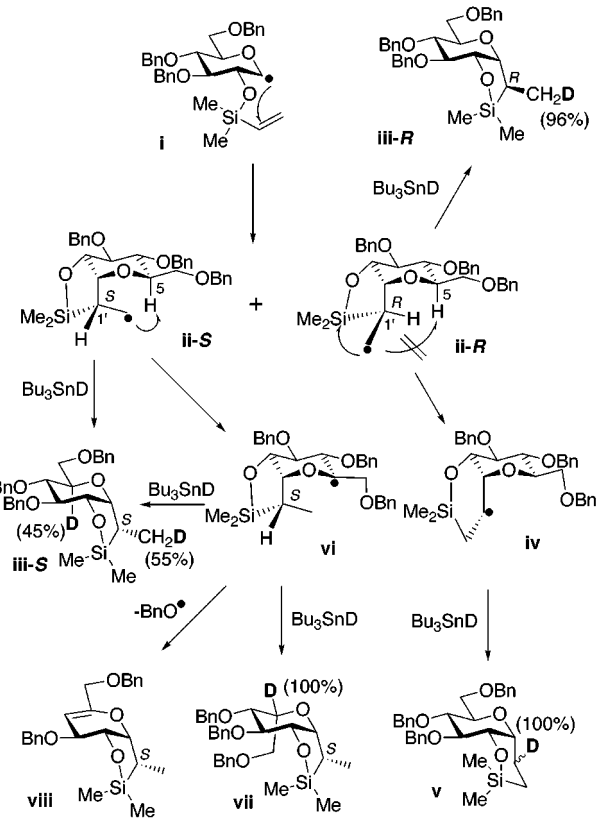
The stereochemistries of **9**, **10**, and **11** were confirmed from their ^{1}H NMR and NOESY spectra and NOE experiments, after converting the compounds into their corresponding acetonides **9′**, **10′**, and **11′** (Figure 2).

A deuterium labeling experiment with Bu_3SnD instead of Bu_3SnH under conditions identical to those in entry 1 was performed, and the positions and rates of deuterium incorporation into the products based on their ^{1}H NMR spectra are shown in Figure 3. These results suggested the reaction pathway shown in Scheme 4, in which the 5-hydrogen abstraction occurs via the 5-*exo*-cyclized 1′*S*-radical **ii-*S***. The anomeric radical **i**, derived from **7**, cyclized to give a mixture of the 5-*exo*-products 1′*S*-radical **ii-*S*** and 1′*R*-radical **ii-*R***, as we expected, a part of which was then trapped with Bu_3SnD to produce **iii-*S*** and **iii-*R***, deuterium-labeled at the methyl group. The radical **ii-*R*** was ring-enlarged into **iv**, which was trapped with Bu_3SnD to give **v** labeled at the position β to the silicon. In the 1′*S*-radical **ii-*S***, the primary radical would be located very close to the 5-position, and accordingly, the 5-hydrogen was abstracted to generate a relatively stable tertiary radical **vi**. The reduction of **vi** by Bu_3SnD from the α- or β-face gave **iii-*S*** and its 5-epimer **vii**, respectively, the 5-positons of which were deuterium-labeled, and an elimination of benzyloxy radical from **vi** would give **viii**.[14] On the basis of this reaction pathway, the 1′-configuration of the benzyloxy-eliminated product **viii** should be *S*.

The radical reaction as described above was unsuccessful, and the results suggested that the conformations of the substrates **7** might be unsuitable for occurring the desired radical ring-enlargement reaction.

(14) A similar 5-hydrogen abstraction has been found during the radical cyclization study with a phenyl 1-seleno-β-D-glucoside attaching an allyl group at the 2-hydroxyl: De Mesmaeker, A.; Waldner, A.; Hoffmann, P.; Winkler, T. *Synlett* **1994**, 330−332.

Scheme 4



The Conformation-Flip Strategy: Radical Reactions with 2-*O*-Vinylsilyl Ethers of Phenyl 3,4,6-Tri-*O*-TBS-1-seleno-D-glucosides as the Substrates. Recently, it was recognized that introducing a significantly bulky protecting group at the 3- and 4-*trans*-hydroxyl groups 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 mutual steric repulsion.[15−18] Suzuki and co-workers first reported this type of conformational feature of pyranosides and efficiently synthesized aryl α-*C*-glycosides using a conformation-flipped donor (Figure 4a).[15] We successfully constructed the tricyclic sugar moiety of herbicidin B, a nucleoside antibiotic, via a facial selective reduction of the enone system of the substrate, the conformation of which was effectively restricted by steric repulsion between the bulky silyl groups on the pyranose ring (Figure 4b).[16] On the basis of these findings, we designed the 3,4-di-*O*-TBS-protected D-glucose derivatives **13** as alternative substrates, which might adopt an unusual $^1C_4$-conformation because of the steric effect of the bulky TBS groups. We assumed that the *exo*-cyclized radical intermediate **x**, derived from an anomeric radical **ix**, would also prefer, due to steric repulsion between the

(15) Hosoya, T.; Ohashi, Y.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **1996**, *37*, 663−666.

(16) Ichikawa, S.; Shuto, S.; Matsuda, A. *J. Am. Chem. Soc.* **1999**, *121*, 10270−10280.

(17) X-ray crystallographic analysis of a 3,4,6-tri-*O*-TBS-glucose derivative in a $^1C_4$-conformation: Walford, C.; Jackson, R. F. W.; Rees, N. H.; Clegg, W.; Heath, S. L. *Chem. Commun.* **1997**, 1855−1856.

(18) For other examples, see: (a) Roush, W. R.; Sebesta, S. P.; Bennett, C. E. *Tetrahedron* **1997**, *53*, 8825−8836. (b) Roush, W. R.; Sebesta, D. P.; James, R. A. *Tetrahedron* **1997**, *53*, 8837−8852. (c) Nunez, R.; Unwalla, R. J.; Cartledge, F. K.; Cho, S. G.; Riches, B. H.; Glenn, M. P.; Hungerford, N. L.; Lambert, L. K.; Brecknell, D. J.; Kitching, W. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1365−1368.

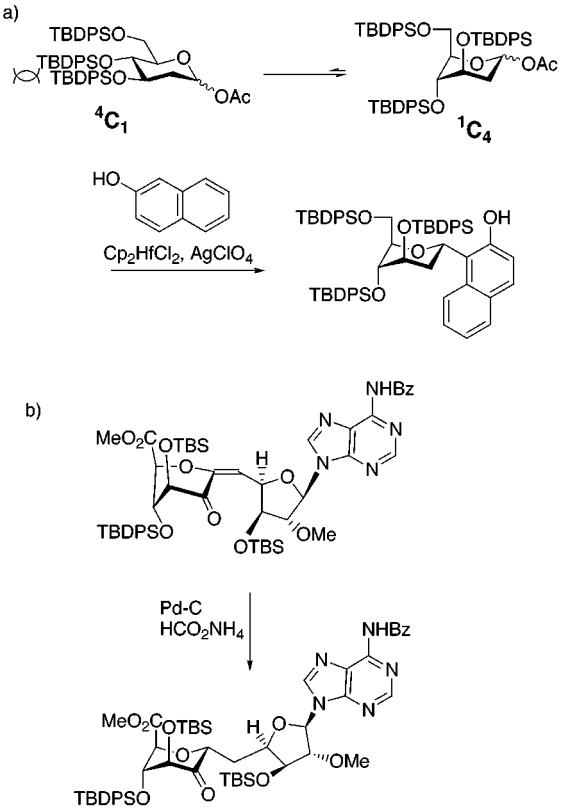


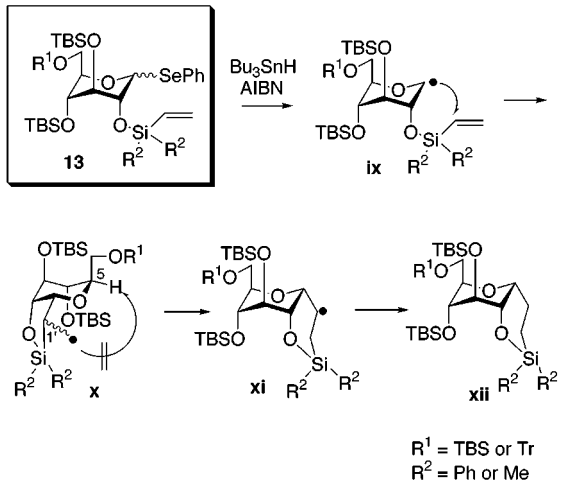
Figure 4.

TBS groups, a $^1C_4$-conformation, in which the primary radical would not be close to the 5-hydrogen. Accordingly, the desired product **xii** would be obtained as the major product via the radical ring-enlargement reaction, without the product of 5-hydrogen abstraction, as shown in Scheme 5.

The substrates were prepared from the known glycal **14**[19] as shown in Scheme 6. The TBS groups were introduced at the 3-, 4-, and 6-hydroxyls of **14**, and the resulting compound **15** was successively treated with dimethyldioxirane and $PhSeH/(CF_3CO)_2O$ in CH_2Cl_2 to give 1-*β*-phenylselenide **16** and 1-α-phenylselenide **17**[20] in 53% and 28% yields, respectively. A dimethyl- and/or diphenylvinylsilyl tether was then introduced at the 2-hydroxyl of the phenylselenides to give **13a**, **13b**, and **13c**, the substrates for the radical reaction. The conformation of the substrate **13a** was investigated by ^1H NMR and compared to that of the previous tri-*O*-benzyl-protected substrate **7** (Figure 5). While the relatively large coupling constants in the benzyl substrate **7** suggest that it has the usual $^4C_1$-conformation (Figure 5a), the rather small coupling constants in the TBS-protected **13a** indicate that it prefers a flipped $^1C_4$-conformation, as expected (Figure 5b).

Radical reactions of **13a**, **13b**, and **13c** were carried out under kinetic [treatment in the presence of Bn_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. The products were isolated as the corresponding pentabenzoates (Scheme 6); the

Scheme 5



results are shown in Table 1. These reactions (entries 4−7) gave the three *C*-glycosidic products, i.e., the 1α-(2-hydroxyethyl)-*C*-glycoside **18** via the 6-*endo*-cyclization product, and the 1α-(1-hydroxyethyl)-*C*-glycosides **19** and **20** via the 5-*exo*-cyclization products, where no products via the 5-hydrogen abstraction reaction were detected. Heating the 2-*O*-dimethylvinylsilyl-*β*-phenylseleno substrate **13a**, having a dimethylvinylsilyl tether, in the presence of Bn_3SnH and AIBN in benzene at 80 °C selectively gave the 1α-(1-hydroxyethyl)-*C*-glycosides **19** and **20**, along with a trace of the 1α-(2-hydroxyethyl)-*C*-glycoside **18** (entry 4, 85%, **18**:**19**:**20** = 6:49:45). When a mixture of Bn_3SnH and AIBN was added slowly to a solution of **13a** in chlorobenzene at 130 °C, the ring-enlargement reaction effectively occurred to give the desired 1α-(2-hydroxyethyl)-*C*-glycoside **18** as the major product (entry 5, 50%, **18**:**19**:**20** = 74:15:11). The yield of the desired **18** was increased in a similar thermodynamic reaction with **13b**, having a diphenylvinylsily tether, as a substrate (entry 6, 63%, **18**:**19**:**20** = 87:6:7). Similar results were obtained with the 2-*O*-diphenylvinylsilyl-α-phenylseleno substrate **13c** (entry 7, 60%, **18**:**19**:**20** = 77:8:15). Thus, this conformation-flip strategy successfully improved the yields of the desired 1α-(2-hydroxyethyl)-*C*-glycoside.

These results demonstrated that the ring-enlargement reaction of a 3-oxa-2-silacyclopentylmethyl radical into a 4-oxa-3-silacyclohexyl radical, which was previously observed in nucleosides and indane derivatives,[11] occurred in this hexopyranose system.

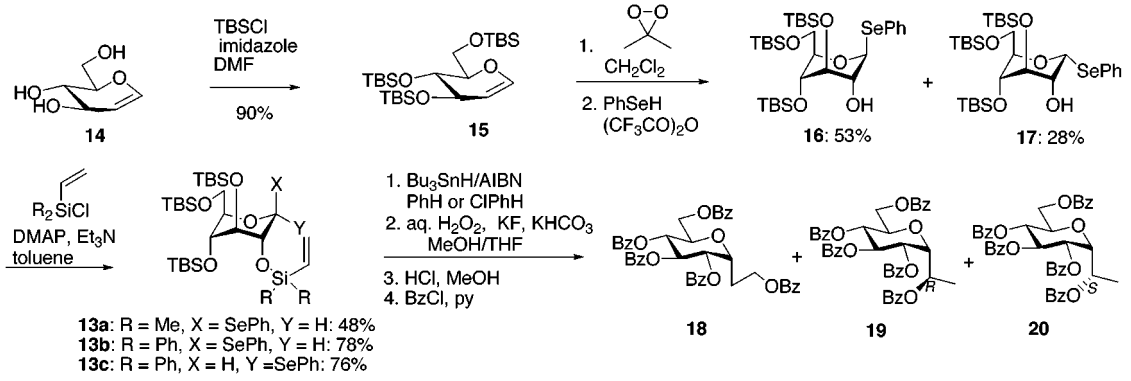
Synthesis of the Potent IP_3 Receptor Ligand 5. Based on the above results, the synthesis of the target compound **5** was next performed, using the radical reaction based on the conformation-flip strategy, as summarized in Scheme 7. To introduce the phosphate units at the desired positions later, selective protection of the hydroxyls of the radical reaction substrate was required. Therefore, we chose phenyl 6-*O*-trityl-3,4-di-*O*-TBS-1-seleno-D-glucoside **24**, with a diphenylvinylsilyl tether at the 2-hydroxy, as the substrate. Two TBS groups were introduced at the free hydroxyls of the known 6-*O*-trityl-glycal **21**[21] by the usual method to give **22**. Oxidation of the glycal **22** with dimethyldioxirane gave the corresponding 1,2-epoxide, which was im-

(19) Friesen, R. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6656−6660.

(20) The anomeric configuration was determined by NOE experiments (400 MHz, pyridine-d_5): when the anomeric proton of **17** was irradiated, an NOE (14.0%) was observed at the 6-protons.

(21) Esswein, A.; Rembold, H.; Schmidt, R. R. *Carbohydr. Res.* **1990**, *200*, 287−305.

Scheme 6



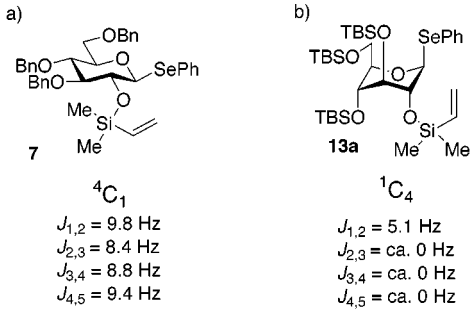
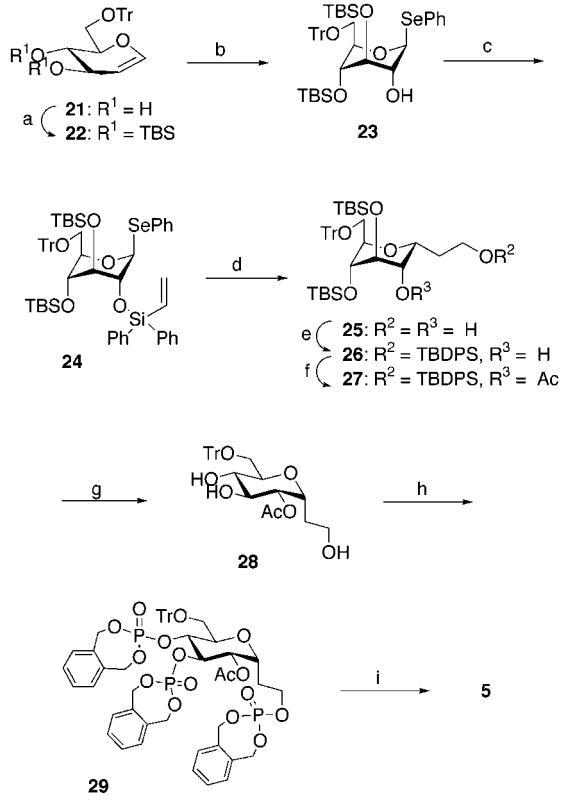


Figure 5.

Scheme 7



Conditions: (a) TBSCl, imidazole, DMF, 60 °C, 85%; (b) (1) dimethyldioxirane, CH_2Cl_2, 0 °C−rt, (2) PhSeH, Et_3N, CH_2Cl_2, 0 °C−rt; (c) diphenylvinylchlorosilane, Et_3N, DMAP, toluene, rt, 56% from **22**; (d) (1) Bu_3SnH, AIBN, ClPhH, reflux, (2) H_2O_2, $NaHCO_3$, aq MeOH/THF, rt, 52%; (e) TBDPSCl, imidazole, DMF, rt, quant, (f) Ac_2O, DMAP, MeCN, 60 °C, quant; (g) TBAF, AcOH, THF, rt, 92%; (h) (1) XEPA, tetrazole, CH_2Cl_2, rt, (2) *m*-CPBA, −40 °C, 77%; (i) (1) H_2, Pd−C, MeOH, rt, (2) TFA, MeOH, rt, (3) aq NaOH, rt, 84%.

mediately treated with PhSeH under basic conditions to give the 1*β*-phenylselenide **23** stereoselectively. The vinylsilyl tether was introduced at the 2-hydroxyl of **23** by the method described above to complete the preparation of the radical reaction substrate **24**. The radical reaction under conditions identical to those for entry 6 in Table 1, and subsequent oxidative treatment without fluoride ion to avoid the undesired removal of the TBS groups, successfully produced the desired 1α-*C*-glycoside **25** in 55% yield. After protecting the primary hydroxyl with a TBDPS group, we next investigated various means of protecting the 2-hydroxyl of compound **26**. Although the protection by a benzyl, THP, or pivaloyl group proved unsuccessful, the corresponding 2-*O*-acetate **27** was obtained quantitatively when **26** was heated with Ac_2O and DMAP at 60 °C in MeCN. The three silyl groups of **27** were removed simultaneously with TBAF to give **28**. Phosphate units were introduced, using the phosphoramidite method with *o*-xylene *N*,*N*-diethylphosphoramidite (XEPA) developed by Watanabe and co-workers.[22] Thus, **28** was treated with XEPA and tetrazole in CH_2Cl_2, followed by oxidation with *m*-CPBA to give the desired trisphosphate derivative **29** in 77% yield. Finally, the *o*-xylene, trityl, and acetyl protecting groups were successively removed with hydrogenation, acidic hydrolysis, and basic hydrolysis to give the target compound **5** in 84% yield as a sodium salt, after treatment with ion-exchange resin.

The binding affinity of the synthesized **5** for the IP_3 receptor of calf cerebella was evaluated in vitro with [^{3}H] IP_3 as a radioligand.[23] Compound **5** significantly inhibited the binding of [^{3}H] IP_3 with an IC_{50} value of 36 nM. It is notable that the binding affinity of the *C*-glycoside trisphosphate **5** was only about 2-fold lower than that of IP_3 itself (IC_{50} = 16 nM), since the previous study showed that the *O*-glycoside trisphosphate **4** was 25-fold lower than IP_3 in the affinity for the receptor.[6b] The different activity between the *C*-glycoside **5** and the *O*-glycoside **4** may not be due to the property of the glycosidic linkage, since the side-chain length of **5** is also different from that of **4**. However, these results clearly show that the *C*-glycoside trisphosphate **5** can be a good lead for designing further useful compounds as IP_3 receptor ligands.

(22) Watanabe, Y.; Komoda, Y.; Ebisuya, K.; Ozaki, S. *Tetrahedron Lett.* **1990**, *31*, 255−256.

(23) The binding affinity was evaluated with "Inositol-1,4,5-Trisphosphate [^{3}H] Radioreceptor Assay Kit" (NEM Life Science Products), according to the procedure described in its catalog.

Conclusion. We have designed and successfully synthesized 3,7-anhydro-D-*glycero*-D-*ido*-octitol 1,5,6-trisphosphate (**5**), as a potential IP_3 receptor ligand. During our synthetic study, we developed a useful method for constructing the α-*C*-glycosidic structure using the radical cyclization reaction with a temporary connecting vinylsilyl tether, in which conformational restriction due to steric repulsion between adjacent bulky protecting groups on a pyranose ring was effectively used. Biological evaluation of **5** showed that it is a potent IP_3 receptor ligand as we expected.

Experimental Section

Chemical shifts of ^1H and ^{13}C spectra are reported in ppm downfield from TMS. The ^1H NMR assignments reported for the key compounds were in agreement with COSY spectra. Thin-layer chromatography was done on Merck coated plate $60F_{254}$. Silica gel chromatography was done on Merck silica gel 5715. HPLC were performed with YMC-Pack (for purification, R&D 5-A, 20 × 250 mm; for analysis, ODS-M80, 4.6 × 250 mm). Reactions were carried out under an argon atmosphere.

Phenyl 3,4,6-Tri-*O*-benzyl-2-*O*-dimethylvinylsilyl-1-seleno-*β*-D-glucopyranoside (7). A mixture of **6** (1.76 g, 3.00 mmol), Et_3N (1.68 mL, 12.0 mmol), DMAP (37 mg, 0.30 mmol), and dimethylvinylchlorosilane (1.65 mL, 12.0 mmol) in toluene (30 mL) was stirred at room temperature for 15 min. The insoluble materials were filtered off with Celite, and the filtrated was partitioned between EtOAc and saturated aqueous NH_4Cl. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane; 1:20 then 1:10) to give **7** (1.91 g, 95%) as an oil: $[\alpha]^{22}_D$ −40.2 °(c 1.99, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) 7.65−7.64 (m, 2 H), 7.33−7.19 (m, 16 H), 7.09−7.08 (m, 2 H), 6.20 (dd, 1 H, *J* = 14.8, 20.4 Hz), 5.94 (dd, 1 H, *J* = 3.7, 14.8 Hz), 5.74 (dd, 1 H, *J* = 3.8, 20.4 Hz), 4.90 (d, 1 H, *J* = 11.5 Hz), 4.85 (d, 1 H, *J* = 11.5 Hz), 4.82 (d, 1 H, *J* = 9.8 Hz), 4.70 (d, 1 H, *J* = 10.8 Hz), 4.57 (d, 1 H, *J* = 11.9 Hz), 4.54 (d, 1 H, *J* = 10.9 Hz), 4.51 (d, 1 H, *J* = 11.9 Hz), 3.76 (dd, 1 H, *J* = 8.4, 9.8 Hz), 3.74 (dd, 1 H, *J* = 2.0, 11.0 Hz), 3.70 (dd, 1 H, *J* = 4.4, 11.0 Hz), 3.65 (dd, 1 H, *J* = 9.4, 9.4 Hz), 3.50 (dd, 1 H, *J* = 8.4, 9.4 Hz), 3.46 (ddd, 1 H, *J* = 2.0, 4.4, 9.4 Hz), 0.23 (s, 3 H), 0.22 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) 138.57, 138.09, 137.87, 137.85, 133.65, 133.02, 129.23, 128.74, 128.17, 128.06, 127.68, 127.57, 127.39, 127.28, 127.08, 126.69, 86.90, 35.35, 80.13, 78.07, 75.02, 74.77, 74.73, 73.26, 68.77; HRMS (FAB, positive) calcd for $C_{37}H_{43}O_5SeSi$ 675.2045, found 675.2030 (MH^+). Anal. Calcd for $C_{37}H_{42}O_5SeSi$: C, 65.96; H, 6.28. Found: C, 65.89; H, 6.40.

Radical Reaction of 7, 13a, 13b, and 13c (Table 1). Method A (Entries 1 and 4). A mixture of a substrate (0.40 mmol), Bu_3SnH (130 μL, 0.48 mmol), and AIBN (40 mg, 0.24 mmol) in benzene (40 mL) was heated under reflux for 20 min, and then the resulting solution was evaporated. A mixture of the residue, aqueous H_2O_2 (30%, 480 μL, 4.0 mmol), KF (240 mg, 4.0 mmol), and $KHCO_3$ (128 mg, 1.3 mmol) in MeOH/THF (1:1, 32 mL) was stirred at room temperature for 15 h. Aqueous $Na_2S_2O_3$ (1 M, 20 mL) was added, and the resulting insoluble materials were filtered off. The filtrate was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc/hexane; 1:3, 2:3, then 4:1) to give a mixture of products as a syrup, which was analyzed by HPLC (75% MeOH, 1.0 mL/min, 260 nm). **Method B (Entries 2, 3, 5, 6, and 7).** To a refluxing solution of a substrate (0.40 mmol) in benzene or chlorobenzene (40 mL) was added slowly over 1 h a mixture of Bu_3SnH (130 μL, 0.48 mmol) and AIBN (40 mg, 0.24 mmol) in the same solvent (40 mL), and then the resulting mixture was evaporated. The residue was treated under Tamao oxidation conditions, purified, and analyzed by the procedure identical to the one described in method A. **Purification of the Products.** The mixture of the products (50 mg) obtained from the reaction in entry 2 was separated by HPLC (aqueous 60% MeCN, 9.9 mL/min, 260 nm) to give pure **8** (10 mg), **9** (6 mg), **10** (3 mg), **11** (8 mg), and **12** (2 mg), respectively.

(2*R*,3*S*,4*R*,5*S*,6*S*)-4,5-Dibenzyloxy-6-benzyloxymethyl-3-hydroxy-2-(2-hydroxyethyl)tetrahydropyran (8): ^1H NMR (500 MHz, $CDCl_3$) 7.46−7.23 (m, 15 H, aromatic), 4.63−4.53 (m, 6 H, benzyl-CH_2), 4.13 (m, 1 H, 2-CH), 4.13 (ddd, 1 H, 6-CH, *J* = 4.5, 4.7, 7.6 Hz), 3.89 (dd, 1 H, 6-CH_2OBn, *J* = 7.6, 10.4 Hz), 3.78 (dq, 2 H, 2-CH_2CH_2OH, *J* = 4.7, 4.7 Hz), 3.75 (dd, 1 H, 4-CH, *J* = 4.5, 4.5 Hz), 3.61 (br s, 1 H, 3-CH), 3.57 (dd, 1 H, 6-CH_2OBn, *J* = 4.7, 10.4 Hz), 3.50 (dd, 1 H, 5-CH, *J* = 4.5, 4.5 Hz), 3.05, 2.65 (each br s, each 1 H, OH x 2), 2.02, 1.74 (each m, each 1 H, 2-CH_2CH_2OH); ^{13}C NMR (125 MHz, $CDCl_3$) 137.84, 137.81, 137.27, 128.58, 128.54, 128.45, 128.03, 127.99, 127.90, 127.84, 127.79, 127.63, 77.13, 74.71, 73.56, 73.28, 72.75, 70.13, 69.59, 67.61, 60.67, 31.51; HRMS (FAB, positive) calcd for $C_{29}H_{35}O_6$ 479.2434, found 479.2431 (MH^+).

(2*R*,3*S*,4R,5*S*,6*R*)-4,5-Dibenzyloxy-6-benzyloxymethyl-3-hydroxy-2-[(1*R*)-1-hydroxyethyl]tetrahydropyran (9): $_1H$ NMR (500 MHz, $CDCl_3$) 7.35−7.23 (m, 15 H, aromatic), 4.64−4.48 (m, 6 H, benzyl-CH_2), 4.11 [dq, 1 H, 2-C*H*(OH)CH_3, *J* = 6.5, 7.4 Hz], 4.07 (m, 1 H, 6-CH), 3.99 (ddd, 1 H, 3-CH, *J* = 2.7, 4.8, 8.0 Hz), 3.79 (t, 1 H, 4-CH, *J* = 4.8 Hz), 3.77 (dd, 1 H, 6-CH_2OBn, *J* = 6.2, 10.0 Hz), 3.67 (dd, 1 H, 6-CH_2OBn, *J* = 5.1, 10.0 Hz), 3.63 (m, 1 H, 5-CH), 3.57 (dd, 1 H, 2-CH, *J* = 2.7, 7.4 Hz), 3.42 (d, 1 H, 3-OH, *J* = 8.0 Hz), 2.84 [br s, 1 H, 2-CH(O*H*)CH_3], 1.27 [d, 3 H, 2-CH(OH)C*H*$_3$, *J* = 6.5 Hz]; ^{13}C NMR (125 MHz, $CDCl_3$) 138.07, 137.78, 137.30, 128.56, 128.50, 128.37, 127.99, 127.92, 127.69, 127.66, 127.62, 77.21, 74.57, 74.25, 73.68, 73.30, 73.09, 72.69, 68.39, 68.05, 67.06, 19.71; HRMS (FAB, positive) calcd for $C_{29}H_{35}O_6$ 479.2434, found 479.2422 (MH^+).

(2*R*,3*S*,4*R*,5*S*,6*R*)-4,5-Dibenzyloxy-6-benzyloxymethyl-3-hydroxy-2-[(1*S*)-1-hydroxyethyl]tetrahydropyran (10): ^1H NMR (500 MHz, $CDCl_3$) 7.34−7.18 (m, 15 H, aromatic), 4.62−4.49 (m, 6 H, benzyl-CH_2), 4.35 (t, 1 H, 6-CH, *J* = 7.0 Hz), 4.04 [ddq, 1 H, 2-C*H*(OH)CH_3, *J* = 0.8, 6.3, 6.6 Hz], 3.85 (dd, 1 H, 6-CH_2OBn, *J* = 7.0, 9.9 Hz), 3.77 (m, 1 H), 3.69 (dd, 1 H, 3-CH, *J* = 2.9, 10.8 Hz), 3.69 (dd, 1 H, 6-CH_2OBn, *J* = 6.6, 9.9 Hz), 3.62 (m, 1 H), 3.50 (dd, 1 H, 2-CH, *J* = 2.9, 6.6 Hz), 3.46 (d, 1 H, 3-OH, *J* = 10.8 Hz), 2.92 [d, 1 H, 2-CH(O*H*)CH_3, *J* = 0.8 Hz], 1.18 [d, 3 H, 2-CH(OH)C*H*$_3$, *J* = 6.3 Hz]; ^{13}C NMR (125 MHz, $CDCl_3$) 137.95, 137.47, 136.93, 130.06, 129.71, 128.96, 128.53, 128.52, 128.38, 128.08, 127.98, 127.92, 127.66, 127.53, 74.60, 74.51, 73.48, 73.25, 72.84, 72.39, 71.86, 67.73, 67.55, 67.45, 17.67; HRMS (FAB, positive) calcd for $C_{29}H_{35}O_6$ 479.2434, found 479.2437 (MH^+).

(2*R*,3*S*,4*R*,5*S*,6*S*)-4,5-Dibenzyloxy-6-benzyloxymethyl-3-hydroxy-2-[(1*S*)-1-hydroxyethyl]tetrahydropyran (11): ^1H NMR (500 MHz, $CDCl_3$) 7.35−7.21 (m, 15 H, aromatic), 4.57−4.41 (m, 6 H, benzyl-CH_2), 4.03 (ddd, 1 H, 6-CH, *J* = 1.5, 6.1, 7.0 Hz), 4.01 [dq, 1 H, 2-C*H*(OH)CH_3, *J* = 6.3, 3.3 Hz], 3.78 (m, 1 H, 4-CH), 3.68 (m, 1 H, 3-CH), 3.65 (dd, 1 H, 6-CH_2OBn, *J* = 6.1, 9.5 Hz), 3.61 (dd, 1 H, 6-CH_2OBn, *J* = 7.0, 9.5 Hz), 3.58 (dd, 1 H, 5-CH, *J* = 1.5, 3.0 Hz), 3.52 (d, 1 H, 3-OH, *J* = 11.6 Hz), 3.45 [d, 1 H, 2-C*H*(OH)CH_3, *J* = 7.3 Hz], 2.88 [br s, 1 H, 2-CH(O*H*)CH_3], 1.17 [d, 3 H, 2-CH(OH)C*H*$_3$, *J* = 6.3 Hz]; ^{13}C NMR (125 MHz, $CDCl_3$) 138.00, 137.66, 136.87, 128.53, 128.40, 128.37, 128.27, 128.01, 127.78, 127.73, 127.62, 80.30, 74.26, 73.61, 73.44, 73.15, 72.35, 72.16, 68.93, 67.66, 67.49, 17.57; HRMS (FAB, positive) calcd for $C_{29}H_{35}O_6$ 479.2434. Found 479.2416 (MH^+).

(2*R*,3*R*,4*S*)-4-Benzyloxy-6-benzyloxymethyl-3,4-dihydro-3-hydroxy-2-[(1*S*)-1-hydroxyethyl]-2*H*-pyran (12): ^1H NMR (500 MHz, $CDCl_3$) 7.40−7.26 (m, 10 H, aromatic), 5.13 (d, 1 H, 5-CH, *J* = 5.0 Hz), 4.67−4.54 (m, 4 H, benzyl-CH_2), 4.17 [dq, 1 H, 2-C*H*(OH)CH_3, *J* = 3.7, 6.4 Hz], 4.04 (d, 1 H, 6-CH_2OBn, *J* = 13.0 Hz), 4.00 (d, 1 H, 6-CH_2OBn, *J* = 13.0 Hz), 3.99 (br s, 1 H, 3-CH), 3.71 (d, 1 H, 2-CH, *J* = 3.7 Hz), 3.73 (dd, 1 H, 6-CH, *J* = 1.9, 5.0 Hz), 3.14 (d, 1 H, 3-OH, *J* = 4.8 Hz), 2.57 (d, 1 H, 1′-OH, *J* = 6.0 Hz), 1.35 [d, 3 H, 2-CH(OH)C*H*$_3$, *J* = 6.4 Hz]; ^{13}C NMR (125 MHz, $CDCl_3$) 153.93, 138.25, 137.88, 128.45, 128.21, 128.05, 127.78, 96.53, 76.17, 72.42, 71.28, 70.17, 69.42, 69.36, 68.52, 19.43.

(1*R*,5*R*,6*R*,8*R*,9*R*,10*S*)-3,3,5-Trimethyl-9,10-dibenzyloxy-8-benzyloxymethyl-bicyclo-[4.4.0]-2,4,7-trioxadecane (Acetonide 9′). A mixture of **9** (16 mg, 0.030 mmol), isopropenyl methyl ether (28 μL, 0.30 mmol), and TsOH·H_2O (1 mg) in DMF (0.5 mL) was stirred at room temperature for 30 min. EtOAc and aqueous saturated $NaHCO_3$ were added, and the whole was partitioned. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane; 1:10 then 1:5) to give **9′** (12 mg, 75%) as a syrup: ^{1}H NMR (500 MHz, $CDCl_3$) 7.38−7.22 (m, 15 H, aromatic), 4.86 (d, 1 H, benzyl-CH_2, J = 11.4 Hz), 4.83 (d, 1 H, benzyl-CH_2, J = 11.6 Hz), 4.74 (d, 1 H, benzyl-CH_2, J = 11.6 Hz), 4.48 (d, 1 H, benzyl-CH_2, J = 11.4 Hz), 4.45 (d, 1 H, benzyl-CH_2, J = 12.2 Hz), 4.39 (d, 1 H, benzyl-CH_2, J = 12.2 Hz), 3.97 (dd, 1 H, 1-CH, J = 5.2, 5.2 Hz), 3.88 (dd, 1 H, 10-CH, J = 5.2, 9.5 Hz), 3.80 (dd, 1 H, 6-CH, J = 5.2, 7.7 Hz), 3.80 (m, 1 H, 8-CH), 3.73 (dd, 1 H, 9-CH, J = 9.5, 9.5 Hz), 3.67 (dq, 1 H, 5-CH, J = 6.3, 7.7 Hz), 3.52 (d, 2 H, 8-CH_2OBn, J = 3.3 Hz), 1.40 (s, 3 H, 3-CH_3), 1.37 (s, 3 H, 3-CH_3), 1.25 (d, 3 H, 5-CH_3, J = 6.3 Hz); HRMS (FAB, positive) calcd for $C_{32}H_{39}O_6$ 519.2746, found 519.2773 (MH^+).

(1*R*,5*S*,6*S*,8*R*,9*R*,10*S*)-3,3,5-Trimethyl-9,10-dibenzyloxy-8-benzyloxymethyl-bicyclo-[4.4.0]-2,4,7-trioxadecane (Acetonide 10′). Compound **10′** (7 mg, 75%) was obtained from **10** (9 mg, 0.02 mmol) as described for the synthesis of **9′** after purification by silica gel column chromatography (EtOAc/hexane; 1:10 then 1:5): ^{1}H NMR (500 MHz, $CDCl_3$) 7.34−7.24 (m, 15 H, aromatic), 4.74 (d, 1 H, benzyl-CH_2, J = 11.4 Hz), 4.66 (d, 1 H, benzyl-CH_2, J = 11.7 Hz), 4.62 (d, 1 H, benzyl-CH_2, J = 11.7 Hz), 4.55 (d, 1 H, benzyl-CH_2, J = 12.1 Hz), 4.54 (d, 1 H, benzyl-CH_2, J = 11.4 Hz), 4.47 (d, 1 H, benzyl-CH_2, J = 11.4 Hz), 4.10 (dd, 1 H, 1-CH, J = 1.8, 2.3 Hz), 4.04 (dq, 1 H, 8-CH, J = 3.1, 8.9 Hz), 3.98 (dq, 1 H, 5-CH, J = 1.8, 6.3 Hz), 3.92 (dd, 1 H, 9-CH, J = 6.7, 8.9 Hz), 3.75 (dd, 1 H, 10-CH, J = 2.3, 6.7 Hz), 3.69 (d, 2 H, 8-CH_2Bn, J = 3.1 Hz), 3.56 (dd, 1 H, 6-CH, J = 1.8, 1.8 Hz), 1.44 (s, 3 H, 3-CH_3), 1.43 (s, 3 H, 3-CH_3), 1.27 (s, 3 H, 5-CH_3); HRMS (FAB, positive) calcd for $C_{32}H_{39}O_6$ 519.2746, found 519.2745 (MH^+).

(1*R*,5*S*,6*S*,8*S*,9*R*,10*S*)-3,3,5-Trimethyl-9,10-dibenzyloxy-8-benzyloxymethyl-bicyclo-[4.4.0]-2,4,7-trioxadecane (Acetonide 11′). Compound **11′** (20 mg, quant) was obtained from **11** (18 mg, 0.04 mmol) as described for the synthesis of **9′** after purification by silica gel column chromatography (EtOAc/hexane; 1:10 then 1:5): ^{1}H NMR (500 MHz, $CDCl_3$) 7.36−7.21 (m, 15 H, aromatic), 4.64−4.36 (m, 6 H, benzyl-CH_2), 4.02 (dq, 1 H, 5-CH, J = 1.1, 6.4 Hz), 3.95 (dt, 1 H, 8-CH, J = 0.9, 6.1 Hz), 3.88 (br s, 1 H, 1-CH), 3.76 (br s, 1 H, 10-CH), 3.75 (d, 2 H, 8-CH_2OBn, J = 6.1 Hz), 3.46 (br d, 1 H, 9-CH, J = 0.9 Hz), 3.33 (br d, 1 H, 6-CH, J = 1.1 Hz), 1.45 (s, 3 H, 3-CH_3), 1.44 (s, 3 H, 3-CH_3), 1.28 (d, 3 H, 5-CH_3, J = 6.4 Hz); FRMS (FAB, positive) calcd for $C_{32}H_{39}O_6$ 519.2746, found 519.2744 (MH^+).

Deuterium-Label Experiment of 7 with Bu_3SnD. Compounds **8D** (4 mg, 8%), **9D** (3 mg, 6%), **10D** (8 mg, 17%), and **11D** (5 mg, 10%) were obtained from **7** (67 mg, 0.10 mmol) by the procedure identical to entry 1 in Table 1 described above, with Bu_3SnD instead of Bu_3SnH, after HPLC purification (aqueous 60% MeCN, 9.9 mL/min, 260 nm). **8D**: FAB-HRMS (FAB, positive) calcd for $C_{29}H_{34}DO_6$ 480.2496, found 480.2473 (MH^+). **9D**: HRMS (FAB, positive) calcd for $C_{29}H_{34}DO_6$ 480.2496, found 480.2491 (NH^+). **10D**: FAB-HRMS (FAB, positive) calcd for $C_{29}H_{34}DO_6$ 480.2496, found 480.2482 (MH^+). **11D**: HRMS (FAB, positive) calcd for $C_{29}H_{34}DO_6$ 480.2496, found 480.2487 (MH^+).

(2*R*,3*R*,4*R*)-3,4-Dihydro-3,4-bis-(*tert*-butyldimethylsilyloxy)-2-(*tert*-butyldimethylsilyloxymethyl)-2*H*-pyran (15). A mixture of **14** (1.00 g, 6.84 mmol), imidazole (4.65 g, 68.3 mmol), and TBSCl (5.15 g, 34.2 mmol) in DMF (50 mL) was stirred at 60 °C for 12 h. After diluted with EtOAc, the resulting mixture was washed with water (3×) and brine. The organic layer was dried (Na_2SO_4), evaporated, and purified by silica gel column chromatography (benzene/hexane; 1:4) to give **15** (2.98 g, 90%) as a syrup: ^{1}H NMR (500 MHz, $CDCl_3$) 6.32 (d, 1 H, J = 6.2 Hz), 4.69 (m, 1 H), 3.99 (m, 1 H), 3.93 (dd, 1 H, J = 7.4, 11.2 Hz), 3.89 (dd, 1 H, J = 3.6, 3.6 Hz), 3.80 (dd, 1 H, J = 3.6, 3.6 Hz), 3.76 (dd, 1 H, J = 3.5, 11.2 Hz), 0.93, 0.90, 0.89 (each s, each 9 H), 0.10, 0.10, 0.08, 0.08, 0.06, 0.05 (each s, each 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) 137.98, 96.37, 75.11, 65.23, 61.74, 56.78, 21.00, 20.87, 20.86, 13.45, 13.09, 13.02, −9.20, −9.31, −9.38, −9.69, −10.19, −10.23; HRMS (FAB, positive) calcd for $C_{24}H_{53}O_4Si_3$ 489.3432, found 489.3232 (MH^+).

Phenyl 3,4,6-Tris-(*O*-*tert*-butyldimethylsilyl)-1-seleno-β-D-glucopyranoside (16) and Phenyl 3,4,6-Tris-(*O*-*tert*-butyldimethylsilyl)-1-seleno-α-D-glucopyranoside (17). To a solution of **15** (885 mg, 1.79 mmol) in CH_2Cl_2 (20 mL) was added a solution of dimethyldioxirane (0.05 M in acetone, 80 mL) at 0 °C, and the resulting mixture was stirred at room temperature for 2 h. After the solvent was evaporated, the residue was dissolved in CH_2Cl_2, dried (Na_2SO_4), and evaporated. To a mixture of the residue and PhSeH (3.8 mL, 36 mmol) in CH_2Cl_2 (4 mL) was added $(CF_3CO)_2O$ (22 μL, 0.070 mmol) at −40 °C, and the resulting mixture was stirred at the same temperature for 10 min and then at room temperature for 10 min. The solvent was evaporated, and the residue was purified by silica gel column chromatography (benzene/hexane; 1:2 then 1:1) to give **16** (612 mg, 52%) and **17** (332 mg, 28%) as syrups. **16**: $[\alpha]^{23}_D$ −88.4° (*c* 0.56, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 7.64−7.62 (m, 2 H, aromatic), 7.28−7.23 (m, 3 H, aromatic), 5.48 (d, 1 H, 1-CH, J = 3.1 Hz), 4.49 (m, 1 H, 5-CH), 3.97 (m, 1H), 3.96 (br s, 1 H, 2-OH), 3.93 (dd, 1 H, 4-CH, J = 4.4, 11.2 Hz), 3.90−3.85 (m, 2 H, 6-CH_2), 3.87 (m, 1H), 0.96−0.90 (m, 27 H, *t*-Bu x 3), 0.17−0.06 (m, 18 H, Si−CH_3 x 6); ^{13}C NMR (125 MHz, $CDCl_3$) 133.25, 129.18, 127.37, 83.91, 91.52, 73.25, 69.45, 62.99, 26.34, 26.16, 26.01, 18.62, 18.49, 18.11, −4.22, −4.32, −4.45, −5.00, −5.07. Anal. Calcd for $C_{30}H_{58}O_5SeSi_3$: C, 54.43; H, 8.83. Found: C, 54.31; H, 8.71. **17**: $[\alpha]^{22}_D$ +31.1°(*c* 0.46, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$·D_2O) 7.57−7.55 (m, 2 H, aromatic), 7.19−7.16 (m, 3 H, aromatic), 5.51 (s, 1 H, 1-CH), 3.91 (t, 1 H, 5-CH, J = 6.8 Hz), 3.82 (br s, 1 H, 3-CH), 3.79 (d, 2 H, 6-CH_2, J = 6.8 Hz), 3.71 (br s, 1 H, 4-CH), 3.66 (br s, 1 H, 2-CH), 0.87, 0.79, 0.78 (each s, each 9 H, *t*-Bu), 0.04−0.09 (m, 18 H, Si−CH_3 x 6); ^{13}C NMR (125 MHz, $CDCl_3$) 132.84, 130.76, 128.95, 127.05, 81.42, 80.68, 72.87, 71.36, 68.97, 60.85, 25.89, 25.79, 25.75, 18.24, 17.97, 17.96, −4.74, −4.85, −4.93, −5.39. Anal. Calcd for $C_{30}H_{58}O_5SeSi_3$: C, 54.43; H, 8.83. Found: C, 54.35; H, 8.74.

Phenyl 3,4,6-Tris-*O*-(*tert*-butyldimethylsilyl)-2-*O*-dimethylvinylsilyl-1-seleno-β-D-glucopyranoside (13a). Compound **13a** (213 mg, 48%) was obtained from **16** (400 mg, 0.60 mmol) as described for the synthesis of **7** after purification by silica gel column chromatography (benzene/hexane; 1:8): $[\alpha]^{22}_D$ −3.8° (*c* 0.93, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 7.43−7.41 (m, 2 H, aromatic), 7.08−7.04 (m, 3 H, aromatic), 5.96 (dd, 1 H, vinyl, J = 14.9, 20.4 Hz), 5.79 (dd, 1 H, vinyl, J = 3.8, 14.9 Hz), 5.57 (dd, 1 H, vinyl, J = 3.8, 20.4 Hz), 5.09 (d, 1 H, 1-CH, J = 6.7 Hz), 3.76 (br d, 1 H, 2-CH, J = 6.7 Hz), 3.79−3.61 (m, 5 H), 0.74−0.70 (m, 27 H, *t*-Bu × 3), 0.06- −0.03 (m, 24 H, Si−CH_3 x 8); ^{13}C NMR (125 MHz, $CDCl_3$) 137.96, 133.48, 133.12, 132.77, 131.24, 128.80, 128.59, 126.72, 83.37, 83.28, 75.97, 74.54, 69.53, 63.85, 26.05, 25.99, 25.74, 18.17, 18.02, 17.86, −1.07, −1.31, −4.41, −4.55, −4.58, −4.67, −5.25; HRMS (FAB, positive) calcd for $C_{34}H_{67}O_5SeSi_4$ 746.3153, found 746.3140 (MH^+). Anal. Calcd for $C_{34}H_{66}O_5SeSi_4$: C, 54.73; H, 8.91. Found: C, 54.89; H, 9.07.

Phenyl 3,4,6-Tris-(*O*-*tert*-butyldimethylsilyl)-2-*O*-diphenylvinylsilyl-1-seleno-β-D-glucopyranoside (13b). Compound **13b** (198 mg, 78%) was obtained from **16** (198 mg, 0.30 mmol) as described for the synthesis of **7**, with diphenylvinylchlorosilane instead of dimethylvinylchlorosilane, after purification by silica gel column chromatography (benzene/hexane; 1:8 then 1:5): $[\alpha]^{23}_D$ −10.5°(*c* 0.93, $CHCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) 7.60−7.59 (m, 4 H, aromatic), 7.42−7.30 (m, 9 H, aromatic), 7.19−7.17 (m, 2 H, aromatic), 6.47 (dd, 1 H, vinyl, J = 14.9, 20.5 Hz), 6.23 (dd, 1 H, vinyl, J = 3.7, 14.9 Hz), 5.85 (dd, 1 H, vinyl, J = 3.7, 20.5 Hz), 5.39 (d, 1 H, 1-CH, J = 5.1 Hz), 4.20 (br d, 1 H, 2-CH, J = 5.1 Hz), 3.98 (br s, 1 H, 4-CH), 3.97 (m, 1 H, 5-CH), 3.92 (br s, 1 H, 3-CH), 3.91 (dd, 1 H, 6-CH_2, J = 7.2, 12.8 Hz), 3.79 (dd, 1 H, 6-CH_2, J = 8.4, 12.8

Hz), 0.89, 0.84, 0.84 (each s, each 9 H, *t*-Bu), 0.09- −0.03 (m, 18 H, Si−CH_3 x 6); ^{13}C NMR (125 MHz, $CDCl_3$) 137.55, 135.25, 134.57, 135.42, 134.27, 133.60, 132.93, 131.66, 129.88, 129.84, 128.67, 127.92, 127.70, 127.66, 126.71, 83.76, 82.19, 76.25, 76.05, 69.90, 63.76, 25.96, 25.88, 25.80, 18.34, 17.97, 17.90, −4.39, −4.61, −4.68, −4.73, −5.14, −5.27; HRMS (FAB, positive) calcd for $C_{44}H_{71}O_5SeSi_4$ 871.3544, found 871.3553 (MH^+). Anal. Calcd for $C_{44}H_{70}O_5SeSi_4$: C, 60.72; H, 8.11. Found: C, 60.95; H, 7.97.

Phenyl 3,4,6-Tris-(*O*-*tert*-butyldimethylsilyl)-2-*O*-diphenylvinylsilyl-1-seleno-α-D-glucopyranoside (13c). Compound **13c** (65 mg, 76%) was obtained from **17** (65 mg, 0.097 mmol) as described for the synthesis of **7**, with diphenylvinylchlorosilane instead of dimethylvinylchlorosilane, after purification by silica gel column chromatography (benzene/hexane; 1:8 then 1:5): ^{1}H NMR (500 MHz, $CDCl_3$) 7.72−7.59 (m, 6 H, aromatic), 7.39−7.33 (m, 7 H, aromatic), 7.19−7.17 (m, 2 H, aromatic), 6.63 (dd, 1 H, vinyl, J = 15.0, 20.5 Hz), 6.30 (dd, 1 H, vinyl, J = 3.6, 15.0 Hz), 5.89 (dd, 1 H, vinyl, J = 3.6, 20.5 Hz), 5.83 (d, 1 H, 1-CH, J = 4.3 Hz), 4.20 (ddd, 1 H, 5-CH, J = 1.0, 3.7, 3.8 Hz), 4.17 (m, 1 H, 2-CH), 3.88 (d, 1 H, 3-CH, J = 8.7 Hz), 3.83 (dd, 1 H, 6-CH_2, J = 1.0, 11.6 Hz), 3.79 (dd, 1 H, 6-CH_2, J = 3.8, 11.6 Hz), 3.76 (d, 1 H, 4-CH, J = 3.7 Hz), 0.85, 0.79, 0.76 (each s, each 9 H, *t*-Bu), 0.06 to −0.20 (m, 18 H, Si−CH_3 × 6); ^{13}C NMR (125 MHz, $CDCl_3$) 137.84, 135.64, 135.61, 134.75, 133.78, 133.67, 133.40, 133.06, 131.53, 130.14, 130.09, 129.75, 128.55, 127.81, 127.74, 126.58, 86.63, 75.83, 74.61, 73.72, 72.32, 62.56, 25.96, 25.92, 25.76, 18.40, 18.02, 17.80, −3.61, −4.30, −4.59, −5.00, −5.07, −5.41; HRMS (FAB, positive) calcd for $C_{44}H_{70}O_5SeSi_4Na$ 893.3364, found 893.3337 (MNa^+).

(2*R*,3*S*,4*S*,5*R*,6*R*)-3,4,5-Tribenzoyloxy-2-(2-benzoyloxyethyl)tetrahydropyran (18), (2*R*,3*S*,4*S*,5*R*,6*R*)-3,4,5-Tribenzoyloxy-2-[(1*R*)-1-benzoyloxyethyl]-6-benzoyloxymethyltetrahydropyran (19), and (2*R*,3*S*,4*S*,5*R*,6*R*)-3,4,5-Tribenzoyloxy-2-[(1*S*)-1-benzoyloxyethyl]-6-benzoyloxymethyltetrahydropyran (20). The radical reaction and subsequent Tamao oxidation were carried out by the procedure described above for **7**. To the resulting reaction mixture after the Tamao oxidation was added saturated aqueous $Na_2S_2O_3$, and the resulting insoluble salts were filtered off. After the filtrate was evaporated, the residue was dissolved in a solution of HCl in MeOH [prepared from AcCl (600 μL) and MeOH (12 mL) at 0 °C]. The resulting mixture was stirred at room temperature for 1.5 h, and then the solvent was evaporated. A mixture of the residue and BzCl (1.8 mL, 15.5 mmol) in pyridine (12 mL) was stirred at room temperature for 50 h. After MeOH was added, the resulting mixture was evaporated, and the residue was partitioned between EtOAc and water. The organic layer was washed with aqueous HCl (0.1 M) and brine, dried (Na_2SO_4), and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane; 1:20, 1:10, then 1:8) to give a mixture of **18**, **19**, and **20**, which was analyzed by HPLC (75% MeOH, 1.0 mL/min, 260 nm). **Purification of the Products.** The mixture of the pentabenzoyl products (25 mg) obtained from the reaction in entry 5 was separated by HPLC (60% MeCN, 9.9 mL/min, 260 nm) to give pure **18** (15 mg), **19** (3 mg), **20** (2 mg), respectively. **18**: ^{1}H NMR (500 MHz, $CDCl_3$) 8.05−7.26 (m, 25 H, aromatic), 5.98 (dd, 1 H, 4-CH, J = 8.3, 8.3 Hz), 5.57 (dd, 1 H, 5-CH, J = 8.3, 8.3 Hz), 5.54 (dd, 1 H, 3-CH, J = 5.2, 8.3 Hz), 4.76 (ddd, 1 H, 2-CH, J = 3.6, 5.2, 11.2 Hz), 4.64 (dd, 1 H, 6-CH_2OBz, J = 6.6, 12.0 Hz), 4.60 (ddd, 1 H, 2-CH_2C*H*$_2$OBz, J = 4.8, 7.4, 11.2 Hz), 4.55 (dd, 1 H, 6-CH_2OBz, J = 3.1, 12.0 Hz), 4.43 (ddd, 1 H, 6-CH, J = 3.1, 6.6, 8.3 Hz), 4.42 (m, 1 H, 2-CH_2C*H*$_2$OBz), 2.51 (m, 1 H, 2-C*H*$_2$$CH_2$OBz), 2.18 (ddd, 1 H, 2-C*H*$_2$$CH_2$OBz, J = 2.8, 7.7, 15.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 166.33, 166.17, 165.55, 165.33, 165.28, 133.52, 133.41, 133.36, 133.10, 132.98, 129.99, 129.89, 129.87, 129.74, 129.56, 128.90, 128.51, 128.39, 128.36, 128.34, 70.66, 70.37, 70.03, 69.38, 69.20, 62.87, 60.97, 25.94; HRMS (FAB, positive) calcd for $C_{43}H_{37}O_{11}$ 729.2326, found 729.2366 (MH^+). **19**: ^{1}H NMR (500 MHz, $CDCl_3$) 8.06−7.19 (m, 25 H, aromatic), 5.97 (dd, 1 H, 4-CH, J = 5.8, 5.9 Hz), 5.71 [m, 1 H, 2-C*H*(OBz)CH_3], 5.54 (dd, 1 H, 3-CH, J = 3.9, 5.9 Hz), 5.45 (dd, 1 H, 5-CH, J = 5.8, 5.8 Hz), 4.99 (dd, 1 H, 6-C*H*$_2$OBz, J = 7.9, 11.8 Hz), 4.60 (dd, 1 H, 2-CH, J = 3.9, 8.7 Hz), 4.52 (m, 1 H, 6-CH), 4.47 (dd, 1 H, 6-C*H*$_2$OBz, J = 3.6, 11.8 Hz), 1.46 [d, 3 H, 2-CH(OBz)C*H*$_3$, J = 6.2 Hz]; HRMS (FAB, positive) calcd for $C_{43}H_{37}O_{11}$ 729.2326, found 729.2364. (MH^+). **20**: ^{1}H NMR (500 MHz, $CDCl_3$) 8.20−7.25 (m, 25 H, aromatic), 6.27 (dd, 1 H, 4-CH, J = 8.2, 8.2 Hz), 5.69 [m, 1 H, 2-C*H*(OBz)CH_3], 5.68 (m, 1 H, 2-CH), 5.62 (dd, 1 H, 5-CH, J = 8.2, 8.2 Hz), 4.87 (ddd, 1 H, 6-CH, J = 3.7, 5.8, 8.2 Hz), 4.62 (dd, 1 H, 6-C*H*$_2$OBz, J = 5.8, 12.4 Hz), 4.60 (dd, 1 H, 6-C*H*$_2$OBz, J = 3.7, 12.4 Hz), 4.53 (m, 1 H, 3-CH), 1.48 [d, 3 H, 2-CH(OBz)C*H*$_3$, J = 6.5 Hz]; ^{13}C NMR (125 MHz, $CDCl_3$) 166.49, 165.70, 165.47, 133.82, 133.68, 133.56, 133.42, 133.30, 130.25, 130.08, 129.94, 129.32, 129.28, 128.89, 128.82, 128.77, 128.63, 128.61, 128.56, 74.32, 72.82, 71.01, 70.33, 70.19, 69.79, 63.78, 16.5; HRMS (FAB, positive) calcd for $C_{43}H_{37}O_{11}$ 729.2326, found 729.2313.

Synthesis of 20 from 10. A mixture of **10** (21 mg, 0.044 mmol) and Pd−C (10%, 6 mg) in MeOH (2 mL) was shaken under H_2 (3 kg/cm^2) at room temperature for 3 h. After the catalysts were filtered off, the filtrate was evaporated. A mixture of the residue, BzCl (31 μL, 0.27 mmol), and DMAP (3 mg, 0.02 mmol) in pyridine (0.5 mL) was stirred at room temperature for 5 h. The solvent was evaporated, and the residue was partitioned between EtOAc and water. The organic layer was washed with aqueous HCl (0.1 M) and brine, dried (Na_2SO_4), and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane; 1:6) to give **20** (7 mg, 21%), of which ^{1}H NMR spectrum (500 MHz, $CDCl_3$) was identical to that of **20** obtained from **13a**.

(2*R*,3*R*,4*R*)-3,4-Bis(*tert*-butyldimethylsiloxy)-3,4-dihydro-2-(triphenylmethoxymethyl)-2*H*-pyran (22). Compound **22** (4.31 g, 85%) was obtained from **21** (3.24 g, 8.34 mmol) as described for the synthesis of **15** after purification by silica gel column chromatography (benzene/hexane; 1:4): $[\alpha]^{21}_D$ −7.9° (*c* 1.12, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 7.48 (m, 6 H), 7.31−7.19 (m, 9 H), 6.36 (d, 1 H, J = 6.2 Hz), 4.65 (ddd, 1 H, J = 0.8, 3.4, 6.2 Hz), 4.17 (m, 1 H), 3.80 (dd, 1 H, J = 3.4, 3.4 Hz), 3.62 (dd, J = 9.1, 10.6 Hz), 3.58 (dd, 1 H, J = 3.4, 3.4 Hz), 3.14 (dd, 1 H, J = 10.6, 10.6 Hz), 0.8 0−0.05 (m, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$) 144.17, 142.94, 128.79, 127.72, 126.82, 101.42, 86.57, 78.67, 70.84, 66.50, 62.74, 25.82, 25.76, 17.93, −4.33, −4.37, −4.53, −4.67. Anal. Calcd for $C_{37}H_{52}O_4Si_2$: C, 72.03; H, 8.49. Found: C, 71.89; H, 8.48.

Phenyl 3,4-Bis(*O*-*tert*-butyldimethylsilyl)-2-*O*-diphenylvinylsilyl-6-*O*-trityl-1-seleno-β-D-glucopyranoside (24). To a solution of **22** (3.0 g, 4.9 mmol) in CH_2Cl_2 (40 mL) was added a solution of dimethyldioxirane (0.05 M in acetone, 100 mL) at 0 °C, and the resulting mixture was stirred at room temperature for 15 min. After the solvent was evaporated, the residue was dissolved in CH_2Cl_2, dried (Na_2SO_4), and evaporated. To a mixture of the residue and PhSeH (10 mL, 97 mmol) in CH_2Cl_2 (4 mL) was added Et_3N (680 μL, 4.9 mmol) at −20 °C, and the resulting mixture was stirred at the same temperature for 105 min. The solvent was evaporated, and the residue was purified by silica gel flash column chromatography (benzene/hexane; 1:2, 1:1, then 2:1) to give **23** as a syrup. A mixture of **23** obtained, Et_3N (2.68 mL, 19.2 mmol), DMAP (40 mg, 0.32 mmol), and diphenylvinylchlorosilane (4.24 mL, 19.2 mmol) in toluene (30 mL) was stirred at room temperature for 2 h. The resulting mixture was partitioned between EtOAc and saturated aqueous NH_4Cl. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by silica gel column chromatography (benzene/hexane; 1:4) to give **24** (2.65 g, 56%) as a syrup: $[\alpha]^{23}_D$ +1.6° (*c* 0.66, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 7.61−7.17 (m, 30 H), 6.47 (dd, 1 H, J = 14.8, 20.3 Hz), 6.23 (dd, 1 H, J = 3.6, 14.8 Hz), 5.88 (dd, 1 H, J = 3.6, 20.3 Hz), 5.45 (d, 1 H, J = 3.6 Hz), 4.27 (br s, 1 H), 4.06 (ddd, 1 H, J = 4.0, 5.0, 6.5 Hz), 3.85 (br s, 1 H), 3.83 (d, 1 H, J = 5.0 Hz), 3.38 (dd, 1 H, J = 6.5, 9.8 Hz), 3.30 (dd, 1 H, J = 4.0, 9.8 Hz), 0.79, 0.72 (each s, each 9 H), −0.04, −0.13, −0.14, −0.18 (each s, each 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) 144.22, 137.61, 135.22, 134.22, 133.99, 133.44, 132.86, 132.22, 129.98, 129.94, 128.91, 128.76, 127.77, 127.73, 127.68, 126.79, 126.71, 86.58, 84.29, 80.05, 76.75, 76.05, 75.89, 71.54, 65.02, 25.90, 25.76, 17.93, 17.83, −4.21, −4.34, −4.73,

−4.83. Anal. Calcd for $C_{57}H_{70}O_5SeSi_3$: C, 68.57; H, 7.07. Found: C, 68.53; H, 7.21.

(2*R*,3*S*,4*R*,5*R*,6*R*)-4,5-Bis(*tert*-butyldimethylsiloxy)-3-hydroxy-2-(2-hydroxyethyl)-6-(triphenylmethoxymethyl)tetrahydropyran (25). To a refluxing solution of **24** (1.26 g, 1.26 mmol) in chlorobenzene (900 mL) was added slowly over 4 h a mixture of Bu_3SnH (1.02 mL, 3.78 mmol) and AIBN (248 mg, 1.52 mmol) in the same solvent (40 mL), and then the resulting mixture was evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane; 1:50 then 1:4) to give the crude radical reaction product as a syrup. A mixture of the syrup obtained, aqueous H_2O_2 (30%, 1.40 mL, 12.6 mmol), and $NaHCO_3$ (105 mg, 1.25 mmol) in MeOH/THF (1:1, 13 mL) was stirred at room temperature for 11 days. Aqueous $Na_2S_2O_3$ (1 M, 20 mL) was added, and the resulting insoluble materials were filtered off. The filtrate was evaporated under reduced pressure, and the residue was partitioned between EtOAc and water. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane; 5:1 then 1:1) to give **25** (471 mg, 55%) as a syrup: ^{1}H NMR (500 MHz, $CDCl_3$) 7.46−7.44 (m, 6 H, aromatic), 7.30−7.21 (m, 9 H, aromatic), 4.10 (dd, 1 H, 6-CH_2OTr, J = 4.0, 10.4 Hz), 3.90 (dd, 1 H, 2-CH_2, J = 3.5, 9.3 Hz), 3.82 (m, 1 H, 2-CH_2CH_2-OH), 3.78 (m, 1 H, 4-CH), 3.77 (m, 1 H, 2-CH), 3.76 (m, 1 H, 6-CH), 3.54 (d, 1 H, 3-OH, J = 11.6 Hz), 3.40 (d, 1 H, 5-CH, J = 2.6 Hz), 3.16 (dd, 1 H, 3-CH, J = 2.9, 11.6 Hz), 3.07 (dd, 1 H, 6-CH_2OTr, J = 3.7, 10.4 Hz), 2.70 (dd, 1 H, 2-CH_2CH_2O*H*, J = 4.8, 7.2 Hz), 2.10 (m, 1 H, 2-C*H*$_2$CH$_2$OH), 1.65 (m, 1 H, 2-C*H*$_2$CH$_2$OH), 0.91, 0.69 (each s, each 9 H, *t*-Bu), 0.09, 0.08, −0.06, −0.09 (each s, each 3 H, Si−CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 143.99, 128.56, 127.86, 127.02, 86.81, 79.29, 71.34, 70.62, 69.78, 66.53, 60.75, 60.66, 60.37, 25.75, 25.64, 17.97, 17.76, −5.06, −5.07, −5.11, −5.13; HRMS (FAB, positive) calcd for $C_{39}H_{59}O_6Si_2$ 679.3850, found 679.3854 (MH^+).

(2*R*,3*S*,4*R*,5*R*,6*R*)-4,5-Bis(*tert*-butyldimethylsilyloxy)-2-(2-*tert*-butyldiphenylsiloxyethyl)-3-hydroxy-6-(triphenylmethoxymethyl)tetrahydropyran (26). Compound **26** (521 mg, quant) was obtained from **25** (394 mg, 0.58 mmol) by the reaction at room temperature as described for the synthesis of **15** with TBDPSCl (181 μL, 0.70 mmol) instead of TBSCl, after purification by silica gel column chromatography (EtOAc/hexane; 1:50): ^{1}H NMR (500 MHz, $CDCl_3$) 7.62−7.18 (m, 25 H), 3.97 (m, 1 H), 3.97 (m, 1 H), 3.84 (s, 1 H), 3.78 (t, 2 H, J = 6.0 Hz), 3.67 (dd, 1 H, J = 8.0, 10.0 Hz), 3.66 (s, 1 H), 3.47 (d, 1 H, J = 11.6 Hz), 3.36 (dd, 1 H, J = 5.9, 10.0 Hz), 3.21 (d, 1 H, J = 11.6 Hz), 1.97 (m, 1 H), 1.76 (m, 1 H), 0.98, 0.91, 0.71 (each s, each 9 H), 0.11, 0.09, −0.04, −0.06 (each s, each 3 H, Si−CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 144.20, 135.51, 135.49, 134.79, 134.01, 133.97, 129.45, 129.41, 128.67, 127.76, 127.58, 127.56, 126.92, 86.75, 79.19, 71.24, 70.46, 70.11, 64.67, 61.77, 60.62, 26.91, 26.56, 25.79, 25.75, 19.12, 17.96, 17.84, −4.89, −4.93, −5.04, −5.12; LRMS (FAB, positive) *m*/*z* 917 (MH^+). Anal. Calcd for $C_{55}H_{76}O_6Si_3$: C, 72.00; H, 8.35. Found: C, 71.80; H, 8.44.

(2*R*,3*S*,4*R*,5*R*6*R*)-3-Acetoxy-4,5-bis-(*tert*-butyldimethylsilyloxy)-2-(2-*tert*-butyldiphenylsiloxyethyl)-6-(triphenylmethoxymethyl)tetrahydropyran (27). A mixture of **26** (43 mg, 0.047 mmol), Ac_2O (8.9 μL, 0.094 mmol), and DMAP (12 mg, 0.10 mmol) in MeCN (0.5 mL) was stirred at 60 °C for 15 h. The solvent was evaporated, and the residue was partitioned between EtOAc and water. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane; 1:50) to give **27** (44 mg, quant) as a syrup: ^{1}H NMR (500 MHz, $CDCl_3$) 7.60−7.18 (m, 25 H), 4.38 (s, 1 H), 4.09 (m, 1 H), 3.96 (dd, 1 H, J = 6.2, 7.6 Hz), 3.88 (s, 1 H), 3.75 (m, 2 H), 3.61 (s, 1 H), 3.53 (dd, 1 H, J = 7.6, 10.0 Hz), 3.43 (dd, 1 H, J = 6.2, 10.0 Hz), 2.05 (s, 3 H), 1.90, 1.55 (each m, each 1 H), 0.97, 0.87, 0.76 (each s, each 9 H), 0.07, 0.03 (each s, each 3 H), 0.02 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) 170.86, 144.11, 135.40, 133.69, 129.43, 129.37, 128.55, 127.67, 127.50, 126.80, 86.69, 78.62, 72.06, 69.39, 68.95, 62.96, 62.01, 60.40, 60.33, 34.38, 26.88, 25.96, 25.80, 21.15, 21.12, 19.13, 18.20, 17.81, 14.27, −4.55, −4.59, −4.87, −4.90; HRMS (FAB, positive) calcd for $C_{57}H_{78}O_7Si_3Na$ 981.4953. Found 981.4970 (MNa^+).

(2*R*,3*R*,4*S*,5*S*,6*R*)-3-Acetoxy-4,5-dihydroxy-2-(2-hydroxyethyl)-6-(triphenylmethoxymethyl)tetrahydropyran (28). A mixture of **27** (191 mg, 0.119 mmol), TBAF (1 M in THF, 1.39 mL, 1.39 mmol), and AcOH (40 μL, 0.70 mmol) in THF (2 mL) was stirred at room temperature for 24 h. The solvent was evaporated, and the residue was partitioned between EtOAc and water. The organic layer was washed with aqueous saturated NH_4Cl and brine, dried (Na_2SO_4), and evaporated. The residue was purified by silica gel column chromatography (MeOH/$CHCl_3$; 1:50 then 1:15) to give **28** (44 mg, quant) as a syrup: ^{1}H NMR (500 MHz, $CDCl_3$) 7.44−7.22 (m, 15 H), 4.85 (dd, 1 H, J = 5.9, 9.5 Hz), 4.18 (ddd, 1 H, J = 2.7, 5.9, 11.8 Hz), 3.78 (br s, 2 H), 3.76 (m, 1 H), 3.69 (m, 1 H), 3.46 (dd, 1 H, J = 2.9, 9.3 Hz), 3.40 (dd, 1 H, J = 4.2, 10.0 Hz), 3.33 (dd, 1 H, J = 5.9, 10.0 Hz), 2.83 (d, 1 H, J = 2.9 Hz), 2.74 (d, 1 H, J = 2.9 Hz), 2.18 (br s, 1 H), 2.10 (s, 3 H), 2.00, 1.64 (each m, each 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) 170.59, 143.37, 128.54, 127.89, 127.16, 87.43, 73.19, 72.66, 72.27, 71.86, 71.32, 64.63, 60.55, 27.90, 21.04; HRMS (FAB, positive) calcd for $C_{29}H_{33}O_7$ 493.2226. Found 493.2253 (MH^+).

(2*R*,3*S*,4*R*,5*R*,6*R*)-3-Acetoxy-4,5-dihydroxy-6-(triphenylmethoxymethyl)-4,5-bis(*o*-xyloxyphosphoryl)-2-(2-*o*-xyloxyphosphorylethyl)tetrahydropyran (29). XEPA (126 μL, 0.59 mmol) was added to a mixture of **28** (76 mg, 0.15 mmol) and 1*H*-tetrazole (41 mg, 0.59 mmol) in CH_2Cl_2 (4.5 mL) at 0 °C, and the mixture was stirred at room temperature for 30 min. After addition of H_2O (40 μL), the mixture was stirred at room temperature for 10 min. The resulting mixture was cooled to −40 °C, and then *m*-CPBA (130 mg, 0.75 mmol) was added. The mixture was warmed to room temperature over 20 min. The reaction mixture was partitioned between EtOAc (40 mL) and aqueous saturated Na_2SO_3, and the organic layer was washed with water, aqueous saturated $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated. The residue was purified by silica gel column chromatography (EtOAc/$CHCl_3$; 1:4) to give **29** (120 mg, 77%) as a foam: ^{1}H NMR (500 MHz, $CDCl_3$) 7.48−7.13 (m, 27 H, aromatic), 5.46−4.94 (m, 12 H, benzyl-CH_2), 4.77 (t, 1 H, 4-CH, J = 13.7 Hz), 4.62−4.52 (m, 2 H, 3-CH and 5-CH), 4.47−4.41 (m, 3 H, 2-CH and 2-CH_2CH_2-OP), 3.84 (m, 1 H, 6-CH), 3.52 (dd, 1 H, 6-CH_2OP, J = 1.0, 10.3 Hz), 3.43 (dd, 1 H, 6-CH_2OP, J = 7.5, 10.3 Hz), 2.22 (s, 3 H, CH_3CO), 2.14 (m, 1 H, 2-C*H*$_2$CH$_2$OP), 1.13 (m, 1 H, 2-C*H*$_2$-CH_2OP); ^{31}P NMR (125 MHz, D_2O, H-decoupled) 0.21, −1.49, −3.12 (each s); HRMS (FAB, positive) calcd for $C_{53}H_{54}O_{16}P_3$ 1039.2625. Found 1039.2630 (MH^+).

(2*R*,3*S*,4*R*,5*R*,6*R*)-3-Hydroxyl-6-hydroxymethyl-4,5-diphosphoryl-2-(2-phosphorylethyl)tetrahydropyran Hexasodium Salt (3,7-Anhydro-D-*glycero*-D-*ido*-octitol 1,5,6-Trisphosphate Hexasodium Salt, 5). A mixture of **29** (53 mg, 0.051 mmol) and Pd−C (10%, 60 mg) in MeOH (5 mL) was stirred under atmospheric pressure of H_2 at room temperature for 2 h. After the catalysts were filtrated off with Celite, and the filtrate was evaporated. To a solution of the residue in MeOH (1 mL) was added TFA (2 μL, 0.026 mmol) and then evaporated. The residue was dissolved in water and washed with EtOAc (three times), and evaporated. The residue was dissolved in aqueous NaOH (1 M, 4 mL), and the solution was stirred at room temperature for 12 h. The resulting solution was applied to Diaion PK-212 column (H^+ form, developed with H_2O), and the fractions containing **5** (acidic fractions) were evaporated. The residue was dissolved in water−EtOH and evaporated (three times) to remove AcOH. A solution of the residue in water (1 mL) was applied to Diaion WK-20 column (Na^+ form, developed with H_2O), and the fractions containing **5** were evaporated and dried in vacuo to give **5** (sodium salt, 25 mg, 84%) as a white solid: $[\alpha]^{23}_D$ −40.3° (*c* 0.88, H_2O); ^{1}H NMR (400 MHz, D_2O) 4.30 (ddd, 1 H, 4-CH, J = 8.8, 8.8, 8.8 Hz), 4.24 (ddd, 1 H, 2-CH, J = 4.4, 4.4, 5.4 Hz), 3.96 (ddd, 1 H, 5-CH, J = 8.8, 8.8, 8.8 Hz), 3.93−3.89 (m, 3 H, 6-CH_2OP and 2′-CH_2), 3.83 (dd, 1 H, 3-CH, J = 5.4, 8.8 Hz), 3.75−3.72 (m, 2 H, 6-CH_2OP and 6-CH), 2.00 (m, 2 H, 1′-CH_2); ^{13}C NMR (100 MHz, D_2O) 76.71 (d, J_{C-P} = 2.77 Hz),

73.47 (d, $J_{C-P} = 3.69$ Hz), 72.44 (d, $J_{C-P} = 2.77$ Hz), 71.38 (s), 70.88 (d, $J_{C-P} = 1.84$ Hz), 61.34 (d, $J_{C-P} = 5.53$ Hz), 60.64 (s), 26.29 (d, $J_{C-P} = 7.38$ Hz); ^{31}P NMR (125 MHz, D_2O, H-decoupled) 2.68, 2.56, −0.33 (each s); HRMS (FAB, positive) calcd for $C_8H_{14}O_{15}Na_6P_3$ 580.8932, found 580.8914 (MH^+). Anal. Calcd for $C_8H_{13}Na_6O_{15}P_3 \cdot 2H_2O$: C, 15.60; H, 2.78. Found: C, 15.45; H, 2.92.

Acknowledgment. This investigation was supported in part by a Grant from the Ministry of Education, Science, Sports, and Culture of Japan. We acknowledge Dr. A. M. Riley and Prof. B. V. L. Potter, University of Bath, for useful discussions and also Miss T. Iizawa and Drs. M. Takahashi and H. Hotoda, Sankyo Co. Ltd, for the biological evaluation. We are also grateful to Ms. H. Matsumoto, A. Maeda, S. Oka, and N. Hazama, Center for Instrumental Analysis, Hokkaido University, for technical assistance with NMR, MS, and elemental analysis.

Supporting Information Available: ^1H NMR spectral charts of **8**, **9**, **10**, **11**, **12**, **8D**, **9D**, **10D**, **11D**, **9′**, **10′**, **11′**, **13c**, **15**, **18**, **19**, **20**, and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0002339