A Systematic Study of *C*-Glucoside Trisphosphates as *myo*-Inositol Trisphosphate Receptor Ligands. Synthesis of *β*-*C*-Glucoside Trisphosphates Based on the Conformational Restriction Strategy

Masaru Terauchi,[†] Hiroshi Abe,[†] Stephen C. Tovey,[‡] Skarlatos G. Dedos,[‡] Colin W. Taylor,[‡] Michael Paul,[§] Melanie Trusselle,[§] Barry V. L. Potter,[§] Akira Matsuda,[†] and Satoshi Shuto*,[†]

Graduate School of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060-0812, Japan, Department of Pharmacology, Tennis Court Road, University of Cambridge, Cambridge, CB2 1PD, U.K., and Wolfson Laboratory for Medicinal Chemistry, Department of Pharmacy and Pharmacology, University of Bath, Bath BA2 7AY, U.K.

Received October 17, 2005

β-*C*-Glucoside trisphosphates having a C2 side chain (3,7-anhydro-2-deoxy-D-*glycero*-D-*gulo*-octitol 1,5,6-trisphosphate, **11**) and a C3 side chain (4,8-anhydro-2,3-dideoxy-D-*glycero*-D-*gulo*-nonanitol 1,6,7-trisphosphate, **12**) were designed as structurally simplified analogues of a potent D-*myo*-inositol 1,4,5-trisphosphate (IP_3) receptor ligand, adenophostin A. Construction of the *β*-*C*-glucosidic structure, which was the key to their synthesis, was achieved by two different methods based on the conformational restriction strategy: (1) radical cyclization with a temporary connecting silicon tether and (2) silane reduction of glyconolactols having an anomeric allyl substituent. Using these methods, the target *β*-*C*-glycoside trisphosphates **11** and **12** were successfully synthesized. A structure−activity relationship was established on a series of *C*-glucoside trisphosphates, including the previously synthesized related compounds, which were a *C*-glycosidic analogue **3** of adenophostin A, its uracil congener **5**, α-*C*-glucoside trisphosphates **7**−**9** having a C1, C2, or C3 side chain, and the *β*-*C*-glucoside trisphosphates **10**−**12** having a C1, C2, or C3 side chain. The *O*-glycosidic linkage of adenophostin A and its analogues proved to be replaced by the chemically and biologically more stable *C*-glycosidic linkage. The α-C2-glucoside trisphosphate **8** stimulates Ca^{2+} release with a potency similar to that of IP_3 in spite of its simplified structure, indicating a better fit to the receptor than the *β*-C-glucoside trisphosphates and also the α-congeners having a shorter or longer C1 side chain, which was supported by molecular modeling using the ligand binding domain of the IP_3 receptor.

Introduction

D-*myo*-Inositol 1,4,5-trisphosphate (IP_3, **1**, Figure 1) is produced by phospholipase C-catalyzed hydrolysis of phosphatidylinositol 4,5-bisphosphate, which is stimulated by activation of a diverse array of cell-surface receptors. IP_3 has been shown to mobilize Ca^{2+} from the intracellular stores of most mammalian cells.[1] Many IP_3 analogues have been synthesized as specific ligands of IP_3 receptors. Such analogues may be useful in investigating the mechanisms of IP_3-mediated Ca^{2+} signaling and also as leads for developing novel clinically effective drugs.[2,3]

In 1993, adenophostin A (**2**) was isolated from *Penicillium brevicompactum* and shown to be a high-affinity agonist of IP_3 receptors with 10 to ∼100 times higher affinity than IP_3.[4] These results prompted the syntheses of new IP_3 receptor ligands based on the structure of adenophostin A and investigation of the structure−activity relationships of adenophostin A and related compounds.[5−7] The results showed that the D-glucopyranose structure is a good bioisostere of the *myo*-inositol backbone of IP_3, and that the adenine moiety can be replaced by other aromatic rings: the uracil congener **4**, for example, is almost as potent as adenophostin A in stimulating release of Ca^{2+} from intracellular stores.[5] Consequently, we became interested in the *C*-glucosidic trisphosphates as potential IP_3 receptor ligands, because *C*-glycosides can be biologically stable mimics of the corresponding *O*-glycosides.[8] Thus, we previously designed and synthesized the *C*-glycosidic analogue **3** of adenophostin A and its uracil congener **5**.[6d,e] However, their biological effects have not been reported yet.

The three-dimensional positioning of the three phosphate moieties and, in particular, the lone "auxiliary" phosphate group significantly affects the activity of IP_3, adenophostin A, and their derivatives.[5,6] 2-Hydroxyethyl α-D-glucopyranoside 3,4,2′-trisphosphate (**6**) was originally designed and synthesized as a highly simplified analogue of adenophostin A.[7a,b,e] Although the *O*-glycoside trisphosphate **6** is an agonist of the IP_3 receptor, its affinity is more than 10-fold lower than that of IP_3.[5] We hypothesized that the lower affinity of **6** could be due to its side-chain length, which may be too long to allow the phosphate to achieve an effective position for binding. To test this hypothesis, we designed a series of α-*C*-glucoside trisphosphates **7**−**9** having side chains with different lengths, as well as the corresponding *β*-*C*-glucoside trisphosphates **10**−**12**. The *β*-glycosidic structure might be more effective than the α-one, because the lone "auxiliary" phosphate group of IP_3 seems to locate on the *β*-face of the D-glucose backbone when the inositol and pyranose rings are superimposed. In this strategy, it is essential to employ a series of *C*-glycosides as stable mimics of the *O*-glycosides since the corresponding *O*-glycoside trisphosphates (Figure 2) could not be prepared because of their predictable instability due to the "O−C−O−O−P" or "O−C−O−C−O−

* Corresponding author. Tel and fax: 81-11-706-3769. E-mail: shu@pharm.hokudai.ac.jp.
† Hokkaido University.
‡ University of Cambridge.
§ University of Bath.

10.1021/jm051039n CCC: $33.50
Published on Web 02/16/2006

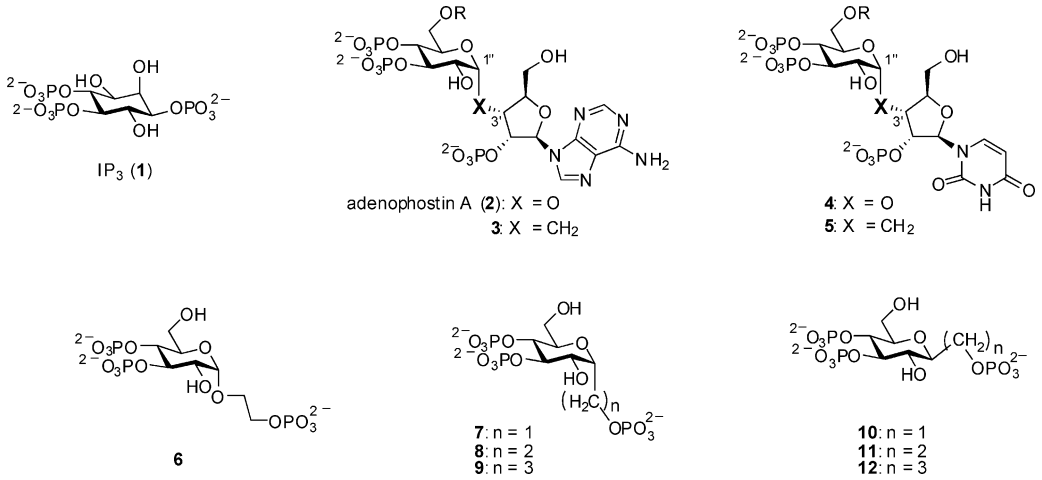


Figure 1. IP$_3$ receptor ligands.

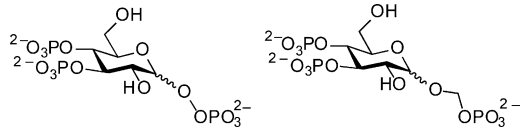


Figure 2. Putatively unstable α-*O*-glucoside trisphosphates.

P" structure. Syntheses of these α-*C*-glycoside trisphosphates **7**−**9** and the *β*-C-glucoside trisphosphate **10** with a C1 side chain have been reported.[6f,g,7c]

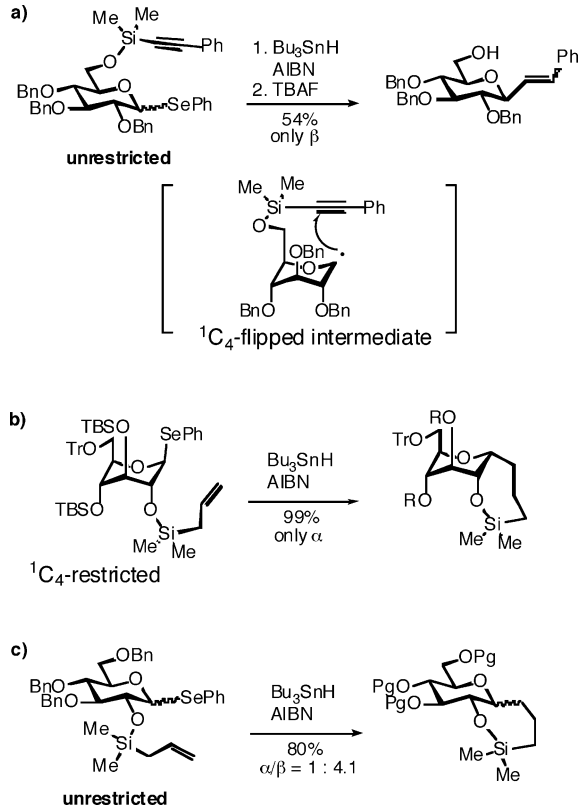
In this paper, we describe the synthesis of the *β*-*C*-glycoside trisphosphate **11** with a C2 side chain and **12** with a C3 side chain, in which the key stereoselective construction of the *β*-*C*-glucosidic structure was achieved by the conformational restriction strategy using an intramolecular radical cyclization or silane reduction at the anomeric position. The results of a systematic biological evaluation of a series of the new and previously synthesized α- and *β*-*C*-glucoside trisphosphates are described, and the structure−activity-relationship is discussed together with molecular modeling.

Results and Discussion

***β*-Selective Radical Cyclization Based on the Conformational Restriction Strategy.** Much attention has been focused on *C*-glycosides because of their importance as stable biologically active mimics for natural *O*-glycosides. Methods for their synthesis have been extensively studied.[8] However, synthesis of *β*-*C*-glycosides is considerably more difficult than synthesis of the corresponding α-*C*-glycosides.[8] Accordingly, effective construction of the *β*-*C*-glycosidic structure should be the key step in the synthesis of the target compounds in this study.

The use of radical reactions is one of the most efficient methods for constructing *C*-glycosidic bonds,[8,9] and therefore we have been working toward the development of stereoselective intramolecular and intermolecular radical *C*-glycosidation reactions.[6d−g,9] Stork and co-workers reported an efficient synthesis of a *β*-*C*-glucoside via a stereoselective radical cyclization using a 2,3,4-tri-*O*-benzyl-protected phenyl l-seleno-*β*-D-glucose derivative having a phenylethynylsilyl group as a radical acceptor tether at the 6-hydroxyl.[10] As shown in Scheme 1a, heating the substrate with Bu$_3$SnH and AIBN in benzene, followed by treatment with TBAF, gave the 2-phenylvinyl *β*-*C*-glucoside in 54% yield. They speculated that the radical cyclization would proceed via a conformationally flipped intermediate (Scheme 1a) in which the tethered hydroxymethyl moiety assumed an axial orientation. With these results in mind, we planned to examine the *β*-selective introduction of C2 and

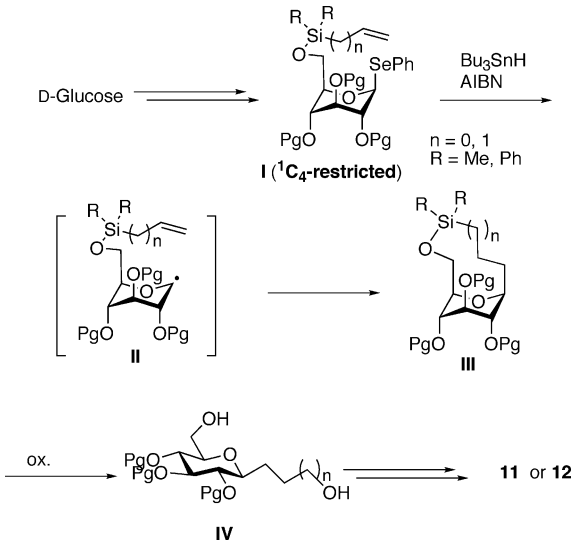
Scheme 1



C3 units by radical reactions with the corresponding 6-*O*-vinylsilyl[11] and 6-*O*-allylsilyl[12] substrates.

We previously investigated the introduction of a C2 and a C3 unit stereoselectively at the anomeric α-position of D-glucose via the radical cyclization with a vinylsilyl or allylsilyl group as a temporary connecting tether.[6f,g] During these studies, we found that the conformational restriction of substrates was effective in realizing highly α-selective reactions.[6f,g,9] When the substrate with the 2-*O*-allylsilyl group conformationally restricted in the unusual ^{1}C$_4$-conformation was used, the desired α-cyclization occurred exclusively (Scheme 1b), while the reaction with the corresponding conformationally unrestricted substrate gave a mixture of the α- and *β*-products (Scheme 1c).[6g,i] A similar highly α-selective radical cyclization also occurred with the ^{1}C$_4$-restricted substrate with 2-*O*-vinylsilyl group to produce the α-*C*-glycoside having an anomeric C2 chain.[6f]

Scheme 2



Based on these findings, we decided to apply the conformational restriction strategy to the synthesis of *β*-*C*-glycosides via radical cyclization reactions.[13] Our synthetic plan is shown in Scheme 2. We designed the 6-*O*-vinylsilyl or *O*-allylsilyl-D-glucose derivative **I**, the conformation of which was restricted in a $^1C_4$-chair form, as the substrate of radical cyclization reactions. Ab initio calculations suggest that the anomeric radical intermediate preferentially assumes the substratelike $^1C_4$-form when the conformations of the precursors of the radical are restricted in an unusual $^1C_4$-chair form.[9a] Therefore, we expected that the radical cyclization using the conformationally $^1C_4$-restricted substrate **I** would stereoselectively form 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 a change of conformation because of the *axial* orientation of the 6-hydroxymethyl moiety bearing the tether, as shown in Scheme 2. The conformational restriction of the substrates to the desired $^1C_4$-form was thought to be possible using significantly bulky silyl protecting groups, as described below. Oxidative cleavage of the Si−C bond of **III** would give the *β*-*C*-glucoside **IV**, which can be converted into the target trisphosphates **11** or **12**.

It is known that introducing a significantly bulky protecting group at the 3,4-*trans*-hydroxyls of pyranoses causes a conformational flip leading to a $^1C_4$-form, in which the bulky substituents are in axial positions due to mutual steric repulsion.[9,14,19] Thus, the 3,4-bis-*O*-silylated substrate **13** having a 6-*O*-vinylsilyl group and **14** having a 6-*O*-allylsilyl group (Figure 3), which should be conformationally restricted in the $^1C_4$-form, were designed for the radical reaction.

The synthesis of the substrates **13** and **14** is summarized in Scheme 3. Starting from D-glucose, phenyl 3,4-bis-*O*-TBS-6-*O*-trityl-l-seleno-*β*-D-glucose (**17**) was prepared according to the previously reported method.[6f] Acetylation of the 2-hydroxyl of **17** and subsequent selective removal of the 6-*O*-trityl group gave **19**. Treatment of **19** with vinyldiphenylchlorosilane, DMAP, and Et_3N in toluene at room temperature quantitatively gave the 6-*O*-vinylsilyl ether **13**, the radical reaction substrate. Similarly, the allyldimethylsilyl group was introduced at the 6-hydroxyl with allyldimethylchlorosilane to give the other substrate **14**.

We also prepared conformationally unrestricted substrates, i.e., the 6-*O*-allyldimethylsilyl and 6-*O*-vinyldiphenylsilyl ethers of phenyl 2,3,4-tri-*O*-benzyl-l-seleno-*β*-D-glucose (**15** and **16**,

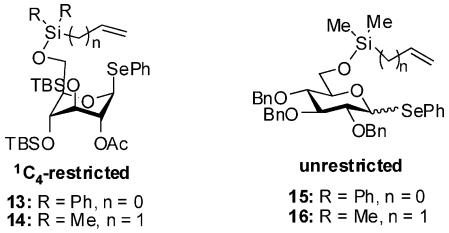


Figure 3. Conformationally restricted and unrestricted substrates for the radical cyclization reaction.

Scheme 3

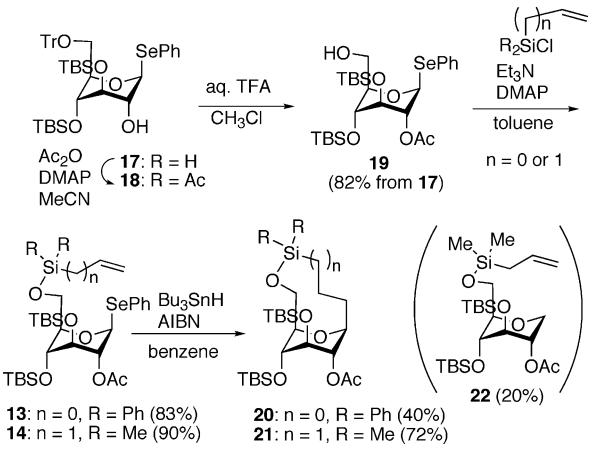


Figure 3), to clarify whether the conformational restriction of substrates in the $^1C_4$-form facilitated the *β*-selective radical cyclization.

The conformations of the substrates **13**−**16** were investigated by ^1H NMR. The unrestricted substrates **15** and **16** had large coupling constants (ca. 9 Hz) between the ring protons 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 **13** and **14** indicated that these preferred the flipped $^1C_4$-like conformation, as expected.[13]

The radical reactions of the $^1C_4$-restricted substrates **13** and **14** as well as the unrestricted substrates **15** and **16** 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 in benzene (80 °C). The reaction was carried out first with the $^1C_4$-restricted vinylsilyl ether **13** and afforded the desired *β*-*endo*-cyclization product **20** in 40% yield. When the $^1C_4$-restricted allylsilyl ether **14** was subjected to the reaction under the same conditions, the *endo*-cyclization effectively occurred to give the desired *β*-product **21** in 72% yield along with the anomeric reduction product **22** in 20% yield. The stereochemistry of the cyclization products **20** and **21** was confirmed by NOE experiments (Figure 4). On the other hand, in the treatment of both of the conformationally unrestricted substrates **15** and **16**, under similar Bu_3SnH/AIBN conditions, many spots were observed on TLC, and none of the cyclization products were obtained.

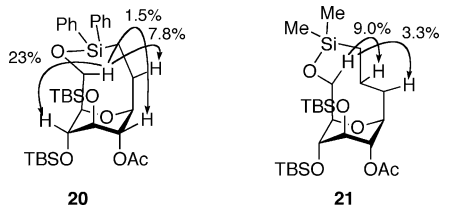
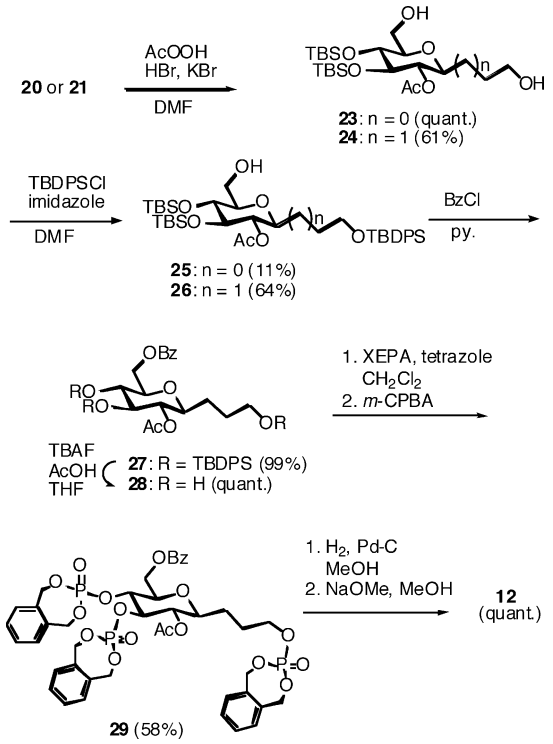


Figure 4. NOE data of the radical cyclization products **20** and **21**.

Scheme 4



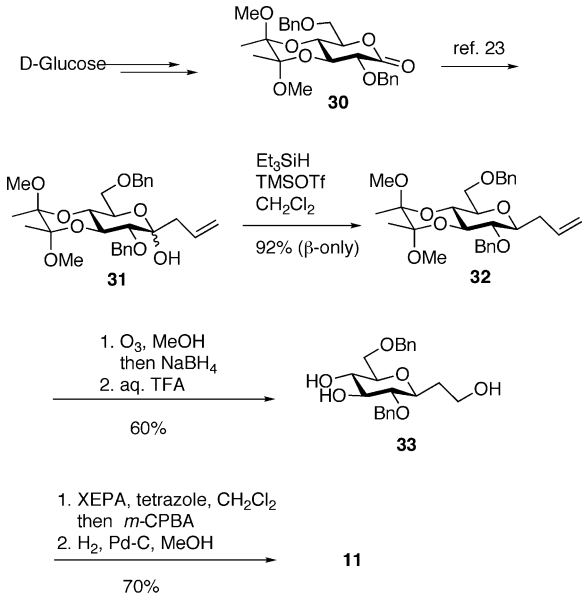
It is worth noting that the reactions of the vinylsilyl and allylsilyl ethers **13** and **14** produced the unusual 8-*endo*- and 9-*endo*-cyclization products **20** and **21**, respectively. These results show that the conformational restriction strategy effectively works in the radical cyclization.

Synthesis of the Target Trisphosphate 12. Conversion of the radical reaction products **20** and **21** into the target trisphosphates **11** and **12** was tried (Scheme 4). The 8-membered ring opening via the oxidative Si−C bond fission, without removing the silyl protecting groups at the 3- and 4-hydroxyls, was achieved by treatment with AcOOH/HBr/KBr in DMF,[15] where the *β-C*-glucosides **23** and **24** were obtained quantitatively and in 61% yield, respectively. Selective silylation of the primary hydroxy on the anomeric chain was next examined. When the hydroxypropyl *C*-glucoside **24** was treated with TBDPSCl/imidazole in DMF at −40 °C, selective silylation occurred to give the desired **26** in 64% yield. Treatment of the hydroxyethyl *C*-glucoside **23** under the same conditions gave the selectively silylated product **25** in only 11% yield. Although we examined selective silylation of **23** under various conditions, the desired **25** was not obtained selectively.

After benzoylation of the 6-hydroxyl of **26**, the three silyl protecting groups were simultaneously removed to give the triol **28**. The phosphate units were introduced, using the phosphoramidite method with *o*-xylene *N*,*N*-diethylphosphoramidite (XEPA).[16] 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 58% yield. Finally, the protecting groups of the phosphates and the hydroxyls were removed by successive hydrogenation and basic hydrolysis to furnish the target **12** quantitatively as a sodium salt, after treatment with ion-exchange resin.

Synthesis of the other target **11** by this route was abandoned because of the very low yield of the anomeric side chain selective silylation of **23**, in which the 6-hydroxyl was preferentially silylated.

Scheme 5



Synthesis of the Target Trisphosphate 11 via Stereoselective Anomeric Silane Reduction with the Conformationally Restricted Substrate. Synthesis of the target **11**, however, was accomplished by another route as shown in Scheme 5, via highly stereoselective anomeric deoxygenation based on the conformational restriction strategy.

Kishi reported an efficient synthesis of *β-C*-glycosides, which involves Grignard addition to a glyconolactone to give usually an anomeric mixture of the corresponding lactols bearing an anomeric substituent that is reduced stereoselectively by trialkylsilane under Lewis acidic conditions to the *β-C*-glycoside.[17] However, the stereochemical outcome of the reduction depends on the sugar structure, and the stereoselectivity is not always high.[17a,d]

We have shown that, in the radical[9] and also the Lewis acid promoted[18] *C*-glycosidation reactions, the anomeric effect[19] can be controlled by manipulating the substrate conformation, and thus, depending on the conformation of the substrates restricted to the $^4C_1$- or the $^1C_4$-form, α- or *β*-selective reactions can occur highly stereoselectively.[9,18] Therefore, we expected that in Kishi's silane reduction the stereoselectivity could also be improved by enhancing the kinetic anomeric effect, when conformationally restricted substrates were employed. The conformation of the transition state and the intermediate can be significantly influenced by conformational effects, which stabilize the ground state conformation.[9,18,20] Accordingly, as shown in Figure 5, in the reduction of substrate **A** conforma-

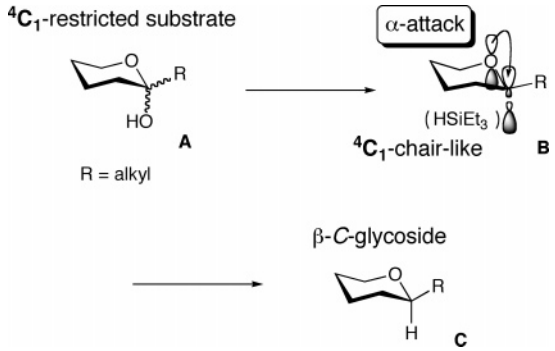
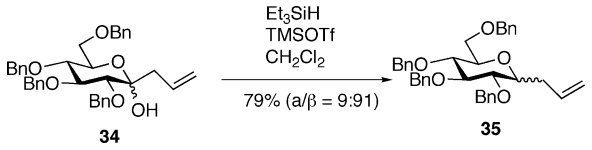


Figure 5. The working hypothesis for the kinetic anomeric effect dependent α-hydride attack forming the *β-C*-glycosides.

Scheme 6



tionally restricted to a $^4C_1$-chair form, the transition state would assume the $^4C_1$-chair-like form **B** due to the conformational restriction of the pyranose backbone, where the anomeric center would be pyramidal. The α-axial attack transition state **B** in the $^4C_1$-restricted form would be significantly stabilized by the kinetic anomeric effect, i.e., the interaction between the antibonding $\sigma^{*\ddagger}$ of the newly forming anomeric C−H bond and the orbital of a nonbonded electron pair (n_O) on the ring oxygen, because of their planar arrangement, to produce the *β-C*-glycoside highly selectively.[21]

Based on this hypothesis, we designed the silane reduction substrate **31** bearing a 3,4-*O*-cyclic-diketal group, the conformation of which would be restricted in the desired $^4C_1$-form due to the *trans*-decalin-type ring system.[6f,g,9,18,22] The substrate **31** was prepared from D-glucose via an addition of CH_2═$CHCH_2$-MgBr on the gluconolactone **30**.[23]

When the substrate **31** was treated with Et_3SiH and TMSOTf in CH_2Cl_2 at −78 °C, the hydride reduction occurred from the α-side with complete stereoselectivity, as we expected, to give the *β-C*-glycoside **32** in 92% yield. We also examined the reduction of the corresponding conformationally unrestricted tetra-*O*-benzyl substrate **34**, where the stereoselectivity and also the yield clearly decreased (α:*β* = 9:91, yield 79%),[21] as shown in Scheme 6. These results demonstrated that the $^4C_1$-conformational restriction effectively improved the stereoselectivity in the Et_3SiH reduction.

Ozonolysis of **32** followed by deprotection with aqueous TFA gave the triol product **33**. Phosphorylation by the phosphoramidite method and subsequent hydrogenation removing the benzyl groups finally afforded the target trisphosphate **11**.

Biological Activity. The ability of a series of *C*-glycosidic compounds, i.e., the *C*-glycosidic adenophostin A analogue **3**, its uracil congener **5**, and the simplified α- and *β-C*-glucoside trisphosphates **7**−**12**, to stimulate opening of the pore of IP_3 receptors was examined. For these analyses, we used recombinant rat type 1 IP_3 receptors stably expressed in chicken B cells that otherwise lack IP_3 receptors and a fluorescent Ca^{2+} indicator trapped within the lumen of the intracellular Ca^{2+} stores to measure the decrease in luminal free [Ca^{2+}] that follows activation of IP_3 receptors.[24−27] The method and its advantages have been recently described.[28] The results are summarized in Table 1, and the potencies are presented relative to both IP_3 (**1**) and adenophostin A (**2**).

Maximal concentrations of the analogues **3**−**5** and **7**−**12**, as well as adenophostin A, examined in this study released the same fraction of the intracellular Ca^{2+} stores (70−80%) as a maximally effective concentration of IP_3 (Table 1), suggesting that each is likely to be a full agonist of the IP_3 receptor. The *C*-glycosidic analogue **3** of adenophostin A was a potent agonist with an EC_{50} value of 4.0 ± 0.2 nM. It was thus some 6-fold more potent than the natural ligand IP_3 (EC_{50} = 24.8 ± 2.1 nM) and only 2-fold less potent than adenophostin A (EC_{50} = 2.1 ± 0.2 nM). The *C*-glycosidic uracil congener **5** was also remarkably active (EC_{50} = 11.3 ± 2.7 nM), being about 2-fold more potent than IP_3 and only 5-fold less potent than adenophostin A. The effect of replacing the *O*-glycosidic linkage with a *C*-glycosidic linkage was similar for adenophostin A (**2** to **3**) and its uracil congener (**4** to **5**); in both cases there was a ∼2-fold decrease in potency. These results show that, irrespective of the attached nucleobase, changing the glycosidic linkage from −O− to −CH_2− is remarkably well tolerated. Insofar as their interactions with IP_3 receptors are concerned, the three-dimensional structures of the *C*-glycosidic analogues **3** and **5** thus seem to be similar to those of the *O*-glycosides **2** and **4**.

Table 1. Effects of Compounds on Ca^{2+} Release via Rat Type 1 IP_3 Receptors Expressed in DT40 Cells[a]

	EC_{50}, nM	Hill slope	Ca^{2+} release, %	*n*	relative potency: **1**	relative potency: **2**
1	24.8 ± 2.1	1.21 ± 0.06	78 ± 2	11	1	0.09 ± 0.01
2	2.1 ± 0.2	1.54 ± 0.13	76 ± 1	12	12.8± 1.3	1
3	4.0 ± 0.2	1.56 ± 0.15	81 ± 2	3	6.2 ± 1.2	0.64 ± 0.05
4	4.6 ± 0.4	1.31 ± 0.08	68 ± 2[a]	4	6.7 ± 2.4	0.43 ± 0.03
5	11.3 ± 2.7	1.40 ± 0.29	79 ± 3	3	2.4 ± 0.6	0.24 ± 0.05
7	394 ± 39	1.07 ± 0.19	73 ± 1	3	0.11 ± 0.03	0.004 ± 0.001
8	49.2 ± 4.3	1.36 ± 0.15	78 ± 1	5	0.43 ± 0.07	0.04 ± 0.01
9	213 ± 37	1.39 ± 0.27	69 ± 2	5	0.12 ± 0.01	0.009 ± 0.001
10	1080 ± 130	0.98 ± 0.12	70 ± 1	5	0.04 ± 0.01	0.002 ± 0.001
11	2040 ± 430	1.51 ± 0.46	71 ± 3	5	0.014 ± 0.003	0.001 ± 0.0002
12	4430 ± 1090	1.51 ± 0.35	64 ± 5	5	0.007 ± 0.001	0.0006 ± 0.0002

[a] The experiments with **4** were performed separately from the others, although again in parallel with **1** (IP_3) and **2** (adenophostin A); the maximal Ca^{2+} release evoked by **1** and **2** in these experiments was 72 ± 2% and 69 ± 3%, respectively. It is therefore clear that maximal concentrations of all the ligands listed were as effective as **1** or **2**.

The simplified α- and *β-C*-glucoside trisphosphates **7**−**12** were all less potent than adenophostin A (Table 1). This accords with previous results showing that aromatic rings such as adenine effectively enhance the potency of adenophostin-related compounds.[5] The activities of these *C*-glucosides were affected by the anomeric α/*β*-stereochemistry. The *β-C*-glucosides were considerably less potent than the corresponding α-*C*-glucosides. The EC_{50} values of the *β-C*-glucosides were > 1 μM, whereas within the α-series, the C2-glucoside **8**, with an EC_{50} value of 49.2 ± 4.3 nM, was almost comparable to that of IP_3.

The α-C2-glucoside **8** was clearly more potent than either its α-C1 **7** (EC_{50} = 394 ± 39 nM) or α-C3 **9** (EC_{50} = 213 ± 37 nM) analogues. Thus, side-chain length markedly affects activity with an optimum chain length of α-C2 in this series. These results suggest that three-dimensional positioning of the "auxiliary" phosphate group in the α-C2-glucoside **8** is suitable for effective receptor binding. It should be noted that **8** is significantly more potent than the simplified *O*-glucoside **6** reported previously, the potency of which is more than 10-fold lower than IP_3,[5,9b] and thus this systematic study with a series of *C*-glucoside trisphosphates represents a "fine-tuning" of activity related to the auxiliary side chain of this long established prototype analogue.

Modeling Study. The α-*C*-glucoside trisphosphate **8**, which is almost as potent as IP_3, can be used to address the binding mode of adenophostin A and its analogues with a pyranose structure. This is because the simplified structure of **8** makes the conformational analysis easier than with adenophostin A and its analogues reported previously.[7d]

We calculated the stable three-dimensional structure of the α-C2-glucoside **8** by MacroModel and compared it with that of IP_3. The initial geometries were generated by a conformational search with the Monte Carlo method and were optimized with MMFFs force field. The results are shown in Figure 6. Both compounds have analogous *trans*-vicinal phosphates on the six-membered chair-form ring, and these moieties are well superimposed, as shown in Figure 6c. However, the third phosphate of the α-C2-glucoside **8** is located at a position significantly different from that of IP_3. These results suggest

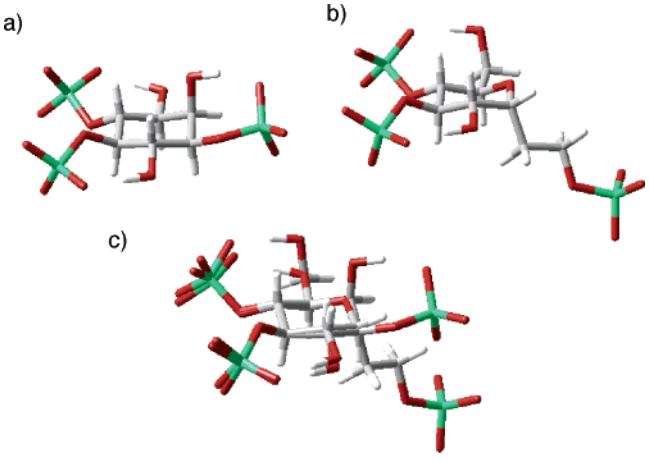


Figure 6. Stable structures of IP_3 (a) and the α-C2-glucoside **8** (b) calculated by MacroModel with MMFFs force field and their superimposition (c).

that the binding mode of the α-C2-glucoside **8** to the receptor might also be different from that of IP_3.

Potential interactions of the α- and *β-C*-glucoside trisphosphates **7**−**12** with the IP_3 receptor binding site were subsequently explored. Superimposition of **8** and IP_3 indicate that the 3,4-vicinal phosphates of the *C*-glucosides attached directly to the ring may bind to the receptor in the same conformation as the 4,5-vicinal phosphates of IP_3. The *C*-glucoside trisphosphates **7**−**12** were built directly into the IP_3 receptor crystal structure using the bound IP_3 as a template. Energy minimization of each system was performed to identify interactions between the ligand and the receptor.

Figure 7shows the modeling of potential interactions of the α-C2-glucoside **8** (Figure 7a) and the *β*-C2-glucoside **11** (Figure 7b) with arginine residues, which recognize the phosphates of IP_3 in the binding site of the IP_3 receptor. IP_3 bound in the crystal structure is also shown (Figure 7c). The *trans*-vicinal phosphate groups of **8** and **11** and the 4- and 5-phosphates of IP_3 have similar conformations; however, it is clear that there are differences between the orientations and interactions of the epimeric side-chain phosphate groups of **8** and **11** and the 1-phosphate group of IP_3. Comparing the conformations of the *C*-glucosides **8** and **11**, it is clear that the most dominant interaction is different between the α- and *β*-glucosides, in that the phosphate group in the α-glucoside **8** points down toward Arg504 and Arg269, whereas it points toward Arg568 in the *β*-glucoside **11**. IP_3 in the crystal structure has a binding mode similar to that of the compound: Arg568 forms hydrogen bonds with the 1-phosphate of IP_3 and also with the side-chain phosphate of **11**. In addition to this, the 1-phosphate group of IP_3 also interacts with Arg504, Asp566 (not shown), and the peptide backbone of Arg568, mediated by crystal waters. It may be postulated that the difference in activity between the α- and *β*-glucosides may be related to the interaction of the phosphate group with different arginine residues. Furthermore, from Figure 7a, a suggestion for the higher activity of the *C*-glucoside **8** may be given in that this is the only glucoside trisphosphate which shows an interaction of the phosphate group with more than one arginine residue, i.e., Arg269 and Arg504. The other two α-*C*-glucosides **7** and **9**, not shown here, show an interaction only with Arg269 and Arg504, respectively. For compound **7** the C1 chain does not seem to be long enough for the phosphate to reach Arg269, and for compound **9** the C3 chain moves the phosphate too far away from Arg504. However, the crystal structure used in this study comprises only the binding domain of the IP_3 receptor. Differences in the observed biological activity might be linked to interactions of ligands with other parts of the receptor.

Conclusion. The synthesis of *β-C*-glucoside trisphosphates **11** and **12** having a C2 side chain or a C3 side chain, designed as structurally simplified analogues of adenophostin A, was achieved. In the synthesis, the key *β-C*-glucosidic structures were effectively constructed based on the conformational restriction strategy using the radical cyclization with a temporary connecting silicon tether or the silane reduction of glyconolactols having an anomeric allyl substituent. We showed that the *O*-glycosidic linkage of adenophostin A and its analogues can be replaced by the chemically and biologically more stable *C*-glycosidic one, and that, in a series of structurally simplified *C*-glucoside trisphosphates related to adenophostin A, the α-C2-glucoside trisphosphate **8** is almost as potent as IP_3 in causing intracellular Ca^{2+} mobilization. This is rationalized in a preliminary fashion using molecular modeling.

Experimental Section

Chemical shifts are reported in ppm downfield from tetramethylsilane (^{1}H and ^{13}C) or H_3PO_4 (^{31}P), and coupling constants are given in Hz. All of the ^{1}H NMR assignments described 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. Reactions were carried out under an argon atmosphere.

Phenyl 2-*O*-Acetyl-3,4-bis-*O*-*tert*-butyldimethylsilyl-1-seleno-*β*-D-glucopyranoside (19). A mixture of **17** (1.6 g, 2.0 mmol), Ac_2O (377 μL, 4.0 mmol) and DMAP (733 mg, 6.0 mmol) in MeCN (20 mL) was stirred at room temperature for 12 h. The mixture was partitioned between AcOEt and H_2O, and the organic layer was washed with brine, dried (Na_2SO_4) and evaporated to give crude **18** (1.7 g, quantitative) as a colorless oil. A mixture of the oil and aqueous TFA (80%, 500 μL) in $CHCl_3$ (5 mL) was stirred at room

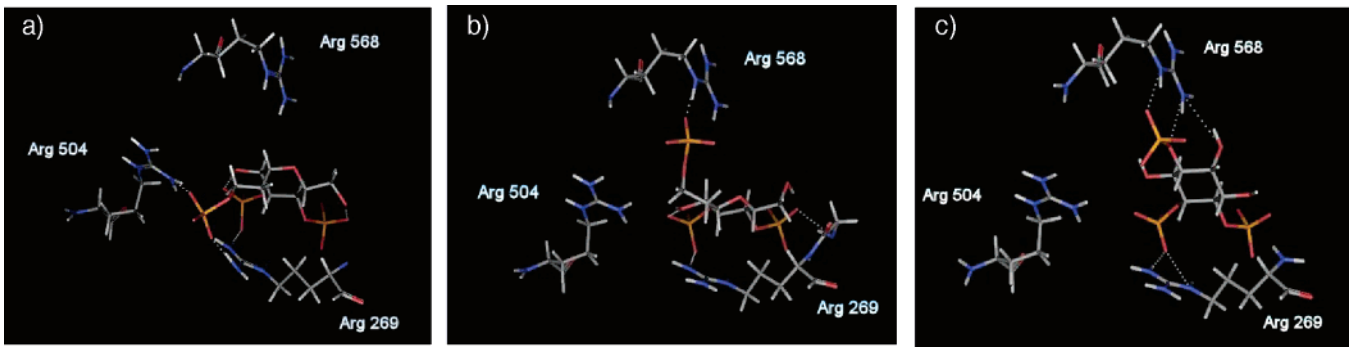


Figure 7. Calculated binding modes of α-C2-glucoside **8**, *β*-C2-glucoside **11**, and IP_3: (a) modeling of potential interactions between the α-*C*-glucoside **8** and arginine residues 504 and 269; (b) the *β-C*-glucoside **11** andArg568; and (c) IP_3 with Arg568 in the ligand binding domain of the IP_3 receptor.

temperature for 1 h and then evaporated. The residue was partitioned between AcOEt and H_2O, and the organic layer was washed with aqueous saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (SiO_2, 5% AcOEt in hexane) to give **19** (1.0 g, 82%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58−7.55 (m, 2 H), 7.27−7.24 (m, 3 H), 5.10 (d, 1 H, J = 8.2), 4.95 (dd, 1 H, J = 5.6, 8.2), 3.79−3.72 (m, 3 H), 3.63−3.58 (m, 3 H), 2.08 (s, 3 H), 0.87 (s, 9 H), 0.86 (s, 9 H), 0.10 (s, 3 H), 0.07 (s, 6 H), 0.06 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 134.5, 133.8, 129.1, 129.0, 127.8, 82.6, 80.5, 74.8, 73.9, 71.0, 62.8, 26.1, 21.6, 18.2, −3.1, −3.3, −3.9, −4.1; LRMS (FAB, positive) m/z 613 (MNa^+). Anal. ($C_{26}H_{46}O_6SeSi_2$): C, H.

Phenyl 2-*O*-Acetyl-3,4-bis-*O*-*tert*-butyldimethylsilyl-6-*O*-diphenylvinylsilyl-1-seleno-β-D-glucopyranoside (13). A mixture of **19** (680 mg, 1.15 mmol), diphenylvinylchlorosilane (305 μL, 1.38 mmol), Et_3N (231 μL, 1.66 mmol), and DMAP (73 mg, 0.60 mmol) in toluene (23 mL) was stirred at room temperature for 30 min. The mixture was partitioned between AcOEt and H_2O, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (SiO_2, 0−2% AcOEt in hexane) to give **13** (760 mg, 83%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63−7.09 (m, 15 H, aromatic), 6.48 (dd, 1 H, vinyl-CH_2, J = 15.0, 20.6), 6.27 (dd, 1 H, vinyl-CH, J = 3.8, 15.0), 5.91 (dd, 1 H, vinyl-CH_2, J = 3.8, 20.6), 5.18 (d, 1 H, H-1, J = 8.2), 4.95 (dd, 1 H, H-2, J = 4.2, 8.2), 4.04 (dd, 1 H, H-6a, J = 5.3, 10.5), 3.92 (dd, 1 H, H-5, J = 6.5, 10.5), 3.80−3.77 (m, 3 H, H-3, −H-4, H-6b), 2.07 (s, 3 H, $-COCH_3$), 0.84 (s, 9 H, -*t*Bu), 0.83 (s, 9 H, -*t*Bu), 0.07 (s, 3 H, $-SiCH_3$), 0.05 (s, 6 H, $-SiCH_3$), −0.02 (s, 3 H, $-SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 134.4, 133.8, 129.1, 129.0, 127.8, 82.6, 80.5, 74.8, 73.9, 71.0, 62.8, 26.1, 21.6, 18.2, −3.1, −3.3, −3.2, −4.1; LRMS (FAB, positive) m/z 821 (MNa^+). Anal. ($C_{40}H_{58}O_6SeSi_3$): C, H.

Phenyl 2-*O*-Acetyl-6-*O*-allyldimethylsilyl-3,4-bis-*O*-*tert*-butyldimethylsilyl-1-seleno-β-D-glucopyranoside (14). Compound **14** (495 mg, 90%) was obtained as a colorless oil from **19** (472 mg, 0.80 mmol) as described for the synthesis of **13** with allyldimethylchlorosilane instead of diphenylvinylchlorosilane: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62−7.57 (m, 2 H, aromatic), 7.34−7.22 (m, 3 H, aromatic), 5.80−5.73 (m, 1 H, allyl-CH), 5.19 (d, 1 H, H-1, J = 7.9), 4.95 (dd, 1 H, H-2, J = 2.0, 7.9), 4.91−4.84 (m, 2 H, allyl-CH_2), 3.90 (dd, 1 H, H-6a, J = 6.2, 9.7), 3.79−3.71 (m, 4 H, G-3, H-4, H-5, H-6b), 2.06 (s, 3 H, $-COCH_3$), 1.62−1.54 (m, 2 H, CH_2═CH−CH_2), 0.91 (s, 9 H, -*t*Bu), 0.90 (s, 9 H, -*t*Bu), 0.12 (s, 3 H, $-SiCH_3$), 0.11 (s, 6 H, $-SiCH_3$), 0.09 (s, 6 H, $-SiCH_3$), 0.08 (s, 3 H, $-SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 134.0, 133.8, 133.3, 129.9, 128.8, 127.3, 113.6, 83.3, 80.0, 77.2, 74.4, 74.3, 70.1, 63.2, 26.2, 26.1, 26.0 24.5, 21.4, 18.2, 18.1, −2.3, −2.3, −3.7, −3.9, −4.2, −4.3; LRMS (FAB, positive) m/z 711 (MNa^+). Anal. ($C_{31}H_{56}O_6SeSi_3$): C, H.

Radical Reaction Product 20. To a refluxing solution of **13** (246 mg, 0.30 mmol) in benzene (60 mL) was added a solution of Bu_3SnH (99 μL, 0.36 mmol) and AIBN (30 mg, 0.18 mmol) in benzene (8.4 mL) dropwise with a syringe pump over 4 h. The resulting mixture was evaporated, and the residue was partitioned between AcOEt and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (SiO_2, 0−2% AcOEt in hexane) to give **20** (77 mg, 40%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63−7.61 (m, 2 H, aromatic), 7.55−7.53 (m, 2 H, aromatic), 7.41−7.24 (m, 6 H, aromatic), 4.57 (br s, 1 H, 2-CH), 4.32 (dd, 1 H, H-6a, J = 11.7, 11.7), 4.08 (m, 1 H, H-5), 3.97 (dd, 1 H, H-1, J = 4.5, 12.1), 3.79 (br s, 1 H, H-4), 3.67 (dd, 1 H, H-6b, J = 4.4, 11.7), 3.49 (br s, 1 H, H-3), 2.38−2.29 (m, 1 H, H-1′a), 2.07 (s, 3 H, $-COCH_3$), 1.99−1.89 (m, 1 H, H-1′b), 1.40−1.20 (m, 2 H, H-2′), 0.89 (s, 9 H, -*t*Bu), 0.64 (s, 9 H, -*t*Bu), 0.08 (s, 3 H, $-CH_3$), 0.04 (s, 3 H, $-CH_3$), 0.03 (s, 3 H, $-CH_3$), −0.01 (s, 3 H, $-CH_3$); LRMS (FAB, positive) m/z 643 (MH^+). Anal. ($C_{34}H_{54}O_6Si_3$): C, H.

Radical Reaction Product 21. Compound **21** (115 mg, 72%) was obtained as a colorless oil from **14** (213 mg, 0.30 mmol) as described for the synthesis of **20**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (s, 1 H, H-2), 4.31 (dd, 1 H, H-6a, J = 8.5, 8.5), 4.15 (d, 1 H, H-5, J = 8.5), 3.87 (d, 1 H, H-4, J = 12.0), 3.66 (d, 1 H, H-3, J = 12.0), 3.50 (d, 1 H, H-6b, J = 8.5), 2.16−2.10 (m, 2 H, H-1, H-1′a), 2.08 (s, 3 H, $-COCH_3$), 1.70−1.65 (m, 2 H, H-2′), 1.52−1.47 (m, 1 H, H-1′b), 0.90 (s, 9 H, -*t*Bu), 0.88 (s, 9 H, -*t*Bu), 0.71 (m, 1 H, H-3′a), 0.58 (m, 1 H, H-3′b), 0.14 (s, 3 H, $-CH_3$), 0.11 (s, 3 H, $-CH_3$), 0.09 (s, 3 H, $-CH_3$), 0.06 (s, 3 H, $-CH_3$), 0.05 (s, 3 H, $-CH_3$), 0.04 (s, 3 H, $-CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 95.8, 77.6, 72.1, 68.3, 62.3, 51.0, 43.2, 26.6, 26.3, 21.4, 18.6, 18.3, 18.2, −0.1, −2.2, −2.8, −3.3, −3.5, −4.8; LRMS (FAB, positive) m/z 533 (MH^+). Anal. ($C_{25}H_{52}O_6Si_3$): C, H.

Radical Reactions of 15 and 16. Compounds **15** and **16** were respectively treated under the radical reaction conditions described for the synthesis of **20**. In both cases, the reaction gave many spots on TLC, and none of the desired cyclization product was obtained.

4-*O*-Acetyl-3,7-anhydro-5,6-bis-*O*-*tert*-butyldimethylsilyl-2-deoxy-D-*glycero*-D-*gulo*-octitol (23). A mixture of **20** (30 mg, 47 μmol), KBr (11 mg, 94 μmol), HBr (30% in AcOH, 3 μL, 12 μmol), and AcOOH (32% in AcOH, 127 μL, 600 μmol) in DMF (1 mL) was stirred at room temperature for 12 h. The mixture was partitioned between AcOEt and H_2O, and the organic layer was washed with aqueous saturated $Na_2S_2O_3$, aqueous saturated $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (SiO_2, 25−50% AcOEt in hexane) to give **23** (23 mg, quantitative) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73 (dd, 1 H, J = 6.2, 8.5), 3.80−3.54 (m, 8 H), 3.48 (ddd, 1 H, J = 2.9, 6.2, 6.4), 2.24 (br s, 1 H), 2.06 (s, 3 H), 1.74−1.68 (m, 2 H), 0.89 (s, 9 H), 0.86 (s, 9 H), 0.10 (s, 3 H), 0.09 (s, 6 H), 0.07 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 81.40, 76.0, 75.5, 74.6, 72.0, 63.2, 60.1, 34.4, 26.2, 26.1, 21.6, 18.2, 18.2, −2.7, −2.8, −3.8, −3.9; LRMS (FAB, positive) m/z 479 (MH^+). Anal. ($C_{22}H_{46}O_7Si_2$): C, H.

5-*O*-Acetyl-4,8-anhydro-6,7-bis-*O*-*tert*-butyldimethylsilyl-2,3-dideoxy-D-*glycero*-D-*gulo*-nonitol (24). Compound **24** (21 mg, 61%) was obtained as a colorless oil from **21** (35 mg, 0.07 mmol) as described for the synthesis of **23**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (br s, 1 H), 3.85 (m, 1 H), 3.66−3.62 (m, 7 H), 2.09 (s, 3 H), 1.94 (br s, 1 H), 1.68−1.59 (m, 3 H), 1.23 (m, 2 H), 0.89 (s, 9 H), 0.87 (s, 9 H), 0.08 (s, 6 H), 0.07 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 93.9, 77.6, 77.2, 72.5, 62.8, 61.8, 26.2, 26.00, 25.7, 21.4, 18.3, 18.1, −3.3, −4.4, −4.5; LRMS (FAB, positive) m/z 515 (MNa^+). Anal. ($C_{23}H_{48}O_7Si_2$): C, H.

4-*O*-Acetyl-3,7-anhydro-5,6-bis-*O*-*tert*-butyldimethylsilyl-1-*O*-*tert*-butyldiphenylsilyl-2-deoxy-D-*glycero*-D-*gulo*-octitol (25). A mixture of **23** (135 mg, 0.28 mmol), TBDPSCl (146 μL, 0.56 mmol), and imidazole (76 mg, 1.1 mmol) in DMF (5 mL) was stirred at −40 °C for 45 min. The mixture was partitioned between AcOEt and H_2O, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (SiO_2, 10−20% AcOEt in hexane) to give **25** (23 mg, 11%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, 4 H, J = 6.8), 7.41−7.35 (m, 6 H), 6.21 (s, 1 H), 3.91−3.77 (m, 4 H), 3.67−3.54 (m, 3 H), 2.13 (m, 2 H), 2.06 (s, 3 H), 2.00 (m, 1 H), 1.78 (m, 1 H), 1.26 (s, 9 H), 0.85 (s, 9 H), 0.84 (s, 9 H), 0.14 (s, 6 H), 0.02 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 135.8, 135.6, 135.5, 135.4, 133.8, 133.3, 129.5, 129.4, 127.6, 127.4, 127.3, 91.7, 77.2, 75.5, 72.7, 69.7, 62.8, 36.6, 27.0, 26.9, 26.1, 26.0, 21.3, 19.5, 18.3, −3.7, −4.5; HRMS (FAB, positive) calcd for $C_{38}H_{64}O_7Si_3Na$ 739.3858 (MNa^+), found 739.3828.

5-*O*-Acetyl-4,8-anhydro-6,7-bis-*O*-*tert*-butyldimethylsilyl-1-*O*-*tert*-butyldiphenylsilyl-2,3-dideoxy-D-*glycero*-D-*gulo*-nonitol (26). Compound **26** (11 mg, 64%) was obtained as a colorless oil from **24** (12 mg, 24 μmol) as described for the synthesis of **25**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, 4 H, J = 6.5), 7.43−7.36 (m, 6 H), 5.92 (br s, 1 H), 3.88 (m, 1 H), 3.68−3.63 (m, 7 H), 2.09 (s, 3 H), 1.95 (br s, 1 H), 1.62−1.44 (m, 4 H), 1.05 (s, 9 H), 0.89 (s, 18 H), 0.10 (s, 9 H), 0.06 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 81.4, 76.0, 75.5, 74.6, 72.0, 63.2, 60.1, 34.4, 26.2, 26.2, 21.6, 18.2, 18.2, −2.7, −2.8, −3.8, −3.9; LRMS (FAB, positive) m/z 753 (MNa^+). Anal. ($C_{39}H_{66}O_7Si_3$): C, H.

5-*O*-Acetyl-4,8-anhydro-9-*O*-benzoyl-6,7-bis-*O*-*tert*-butyldimethylsilyl-1-*O*-*tert*-butyldiphenylsilyl-2,3-dideoxy-D-*glycero*-D-*gulo*-nonitol (27). A mixture of **26** (17 mg, 23 μmol) and BzCl (5.3 μL, 46 μmol) in pyridine (1 mL) was stirred at room temperature for 30 min. The mixture was partitioned between AcOEt and H_2O, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (SiO_2, 10% AcOEt in hexane) to give **27** (19 mg, 99%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02−8.00 (m, 2 H), 7.73−7.65 (m, 4 H), 7.56−7.50 (m, 1 H), 7.44−7.35 (m, 8 H), 6.00 (br s, 1 H), 4.58 (d, 1 H, J = 10.3), 4.35 (m, 1 H), 3.90 (m, 2 H), 3.76 (dd, 1 H, J = 6.5, 6.5), 3.67−3.65 (m, 3 H), 2.07 (s, 3 H), 1.99 (m, 1 H), 1.59 (m, 3 H), 1.04 (s, 9 H), 0.90 (s, 18 H), 0.11 (s, 6 H), 0.07 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 166.1, 135.4, 134.6, 134.4, 133.7, 133.7, 132.8, 130.4, 129.9, 129.6, 129.4, 129.4, 128.7, 128.7, 128.2, 127.6, 127.5, 94.3, 77.6, 77.2, 74.5, 72.6, 63.8, 27.0, 26.7, 26.2, 26.0, 25.9, 25.9, 25.8, 25.8, 25.8, 25.7, 21.3, 19.3, 18.4, 18.1, 18.0, −3.2, −4.3, −4.6; LRMS (FAB, positive) *m*/*z* 857 (MNa^+). Anal. ($C_{46}H_{70}O_8Si_3$): C, H.

5-*O*-Acetyl-4,8-anhydro-9-*O*-benzoyl-2,3-dideoxy-D-*glycero*-D-*gulo*-nonitol (28). A mixture of **27** (19 mg, 23 μmol), TBAF (1 M in THF, 46 μL, 46 μmol), and AcOH (13 μL, 23 μmol) in THF (1 mL) was stirred at room temperature for 48 h. The mixture was evaporated, and the residue was partitioned between AcOEt and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (SiO_2, 25% AcOEt in hexane) to give **28** (8 mg, 99%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, 2 H, J = 7.3, 7.3), 7.58 (dd, 1 H, J = 7.3, 7.3), 7.46 (dd, 2 H, J = 7.3, 7.3), 4.57 (dd, 1 H, J = 3.2, 12.3), 4.37 (dd, 1 H, J = 1.9, 12.3), 4.12 (dd, 1 H, J = 5.3, 9.4), 3.86 (d, 1 H, J = 9.7), 3.68−3.58 (m, 2 H), 3.54 (dd, 1 H, J = 9.7, 9.7), 2.11 (s, 5 H), 1.89−1.82 (m, 1 H), 1.79−1.70 (m, 1 H), 1.58−1.50 (m, 2 H), 1.37−1.25 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 167.6, 133.4, 129.8, 129.1, 128.4, 94.4, 73.3, 70.1, 67.2, 63.6, 62.1, 43.1, 30.9, 21.3, 20.5, 0.2; LRMS (FAB, positive) *m*/*z* 391 (MNa^+). Anal. ($C_{18}H_{24}O_8$): C, H.

4,8-Anhydro-2,3-dideoxy-D-*glycero*-D-*gulo*-nonitol 1,6,7-Trisphosphate Derivative 29. A mixture of **28** (28 mg, 76 μmol), XEPA (73 mg, 304 μmol) and 1*H*-tetrazole (27 mg, 38 μmol) in CH_2Cl_2 was stirred at 0 °C for 30 min. After addition of H_2O (20 μL), the mixture was stirred at room temperature for 10 min. The resulting mixture was cooled to −40 °C, and then *m*-CPBA (70 mg, 400 μmol) was added. The mixture was warmed to room temperature over 30 min and then partitioned between AcOEt and aqueous saturated $Na_2S_2O_3$. The organic layer was washed with H_2O, aqueous saturated $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (SiO_2, 10% MeOH in $CHCl_3$) to give **29** (40 mg, 58%) as a yellow foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03−8.01 (m, 2 H), 7.53−7.11 (m, 15 H), 5.40−4.97 (m, 16 H), 4.71 (dd, 1 H, J = 2.1, 12.3), 4.50 (dd, 1 H, J = 4.1, 12.3), 4.23−4.14 (m, 3 H), 2.59−2.55 (m, 1 H), 2.12 (s, 3 H), 2.12−2.08 (m, 1 H), 1.98−1.91 (m, 1 H), 1.89−1.80 (m, 1 H), 1.65−1.58 (m, 1 H); ^{31}P NMR (500 MHz, $CDCl_3$, H-decoupled) δ −2.18, −2.54, −5.12 (each s); HRMS (FAB, positive) calcd for $C_{42}H_{46}O_{17}P_3$ 915.1948 (MH^+), found 915.1933.

Sodium 4,8-Anhydro-2,3-dideoxy-D-*glycero*-D-*gulo*-nonitol 1,6,7-Trisphosphate (12). A mixture of **29** (40 mg, 44 μmol) and Pd−C (10%, 52 mg) in MeOH (5 mL) was stirred at room temperature under atmospheric pressure of H_2 for 40 min. The catalysts were filtered off with Celite, and the filtrate was evaporated. A mixture of the residue and NaOMe (28%, 82 μL, 400 μmol) in MeOH (5 mL) was stirred at room temperature for 12 h. The mixture was applied to Diaion PK-212 (H^+-form), and the column was developed with H_2O. The fractions containing **12** (acidic fractions) were evaporated. A solution of the residue was washed with $CHCl_3$ (three times) and was applied to Diaion WK-100 (Na^+ form). The column was developed with H_2O, and the fractions containing **12** were evaporated and dried in vacuo to give **12** (sodium salt, 35 mg, quantitative) as a white solid: ^{1}H NMR (500 MHz, D_2O) δ 4.17 (m, 1 H), 3.90−3.63 (m, 5 H), 3.59−3.49 (m, 3 H), 1.70−1.44 (m, 4 H); ^{13}C NMR (100 MHz, D_2O) δ 77.5, 75.2, 73.3, 73.0, 71.7, 65.5, 26.8, 21.6; ^{31}P NMR (500 MHz, D_2O, H-decoupled) δ 2.56, 2.28, 1.72 (each s); HRMS (FAB, negative) calcd for $C_9H_{17}O_{15}Na_3P_3$ 526.9473 (M^-), found 526.9476.

***β*-*C*-Glycoside 32.** A mixture of **31** (103 mg, 0.2 mmol), Et_3SiH (35 μL, 0.22 mmol), and TMSOTf (40 μL, 0.22 mmol) in CH_2Cl_2 (10 mL) was stirred at −78 °C for 1 h, and then Et_3N (100 μL) was added. The resulting mixture was partitioned between AcOEt and aqueous saturated $NaHCO_3$, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (SiO_2, 15% AcOEt in hexane) to give **32** (92 mg, 92%) as a colorless oil: ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.35−7.25 (m, 10 H), 5.96−5.85 (m, 1 H), 5.11−5.05 (m, 2 H), 4.98 (d, 1 H, J = 10.9), 4.64−4.56 (m, 3 H), 3.89 (dd, 1 H, J = 9.1, 9.7), 3.73 (dd, 1 H, J = 1.8, 11.1), 3.67 (dd, 1 H, J = 5.0, 11.1), 3.66 (dd, 1 H, J = 9.7, 10.2), 3.55 (ddd, 1 H, J = 1.8, 5.0, 10.2), 3.42 (dd, 1 H, J = 9.1, 9.1), 3.41−3.36 (m, 1 H), 3.30 (s, 3 H), 3.21 (s, 3 H), 2.62−2.56 (m, 1 H), 2.37−2.30 (m, 1 H), 1.36 (s, 3 H), 1.29 (s, 3H); HRMS calcd for $C_{29}H_{38}NaO_7$ 521.2513 (MNa^+), found 521.2520.

3,7-Anhydro-4,8-di-*O*-benzyl-2-deoxy-D-*glycero*-D-*gulo*-octitol (33). Ozone-containing oxygen was bubbled into a solution of **32** (100 mg, 0.20 mmol) in MeOH (2 mL) at −20 °C until **32** disappeared on TLC (ca. 20 min). After addition of $NaBH_4$ (23 mg, 0.60 mmol) at the same temperature, the resulting solution was stirred at room temperature for 1 h. The mixture was evaporated, and the residue was purified by column chromatography (SiO_2, 30−50% AcOEt in hexane) to give the crude ozonolysis product (47 mg) as an oil. A mixture of the oil and aqueous TFA (80%, 200 μL) in $CHCl_3$ (2 mL) was stirred at 0 °C for 12 h, and then aqueous saturated $NaHCO_3$ (2 mL) was added. The resulting mixture was partitioned between $CHCl_3$ and the aqueous saturated $NaHCO_3$, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (SiO_2, 10% MeOH in $CHCl_3$) to give **33** (59 mg, 60%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.26 (m, 10 H), 4.83 (d, 1 H, J = 10.8), 4.71 (d, 1 H, J = 10.8), 4.57−4.55 (m, 2 H), 4.17 (br, 1 H), 3.86−3.78−3.63 (m, 9 H), 3.26−3.21 (m, 2 H), 1.98−1.82 (m, 2 H); LRMS (FAB, positive) *m*/*z* 411 (MNa^+). Anal. ($C_{22}H_{28}O_6$): C, H.

Sodium 3,7-Anhydro-2-deoxy-D-*glycero*-D-*gulo*-octitol 1,5,6-Trisphosphate (11). A mixture of **33** (7.6 mg, 20 μmol), XEPA (19 mg, 80 μmol), and 1*H*-tetrazole (7.0 mg, 10 μmol) in CH_2Cl_2 (1 mL) was stirred at 0 °C for 60 min. After addition of H_2O (20 μL), the mixture was stirred at room temperature for 10 min. The resulting mixture was cooled to −40 °C, and then *m*-CPBA (40 mg, 200 μmol) was added. The mixture was warmed to room temperature over 30 min. The reaction mixture was partitioned between AcOEt and aqueous saturated $Na_2S_2O_3$, and the organic layer was washed with H_2O, aqueous saturated $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated. The residue was purified by preparative TLC (SiO_2, 10% MeOH in $CHCl_3$) to give the phosphorylation product as a foam (13 mg). A mixture of a foam and Pd−C (10%, 17 mg) in MeOH (2 mL) was stirred at room temperature under atmospheric pressure of H_2 for 4 h. After filtration of the catalysts with Celite, the filtrate was evaporated. From the residue, compound **11** (sodium salt, 8 mg, 70% from **33**) was obtained as a white solid, as described for the purification of **12**: ^{1}H NMR (500 MHz, D_2O) δ 3. (dd, 1 H, J = 8.4, 17.0), 3.80 (dd, 1 H, J = 8.4, 10.0), 3.78 (dd, 1 H, J = 8.4, 8.8), 3.66−3.12 (m, 6 H), 2.02 (m, 1 H), 1.55 (m, 1 H); ^{13}C NMR (100 MHz, D_2O) δ 81.4, 74.4, 73.3, 70.4, 69.7, 62.1, 33.8, 21.1; ^{31}P NMR (500 MHz, D_2O, H-decoupled) δ 3.11, 2.67, 2.36 (each s); HRMS (FAB) calcd $C_8H_{14}O_{15}Na_6P_3$ 580.8932 (MH^+), found 580.8914.

Modeling Studies. Initial investigations into binding modes of the *C*-glucoside trisphosphates at the IP_3 receptor (PDB code 1N4K) were performed using a docking program (GOLD version 2.2). Docks carried out both in the presence and in the absence of conserved crystal waters gave poor results as the glucose ring was in a very different orientation to the ring of the crystal structure

IP_3 ligand. As an alternative method, simulations of the ligand binding mode for the *C*-glucoside trisphosphates **7**−**12** were carried out using Molecular Operating Environment (MOE 2004.03). The basic assumption behind this study was that the two phosphate groups attached directly to the ring bind in the same conformation as the 4- and 5-position phosphate groups of IP_3. Therefore, it was logical to use the crystal structure conformation of IP_3 bound to the IP_3 receptor as a starting point for building these molecules. Heavy atoms of the IP_3 binding site (PDB code 1N4K) and associated water molecules were fixed, and hydrogen atoms were added. The system was energy-minimized using the MMFF94 force field in MOE to remove any clashes between the newly added hydrogen atoms. A series of modifications were implemented to transform the IP_3 structure into the six *C*-glycoside trisphosphates. These can be summarized as follows: (i) replacement of carbon at position 2 with oxygen; (ii) replacement of OH attached at the 3-position with CH_2OH; (iii) addition of appropriate $(CH_2)_nOPO_3^{2-}$, where $n = 1$, 2, or 3 in the correct position to form the three α-*C*-glucoside and three *β*-*C*-glucoside polyphosphates **7**−**12**. The system was energy-minimized following each transformation. Once the desired structures had been built, observation of the resulting conformations suggested possible interactions with three arginine residues across the α- and *β*-*C*-glucosidic compounds, namely, Arg269 and Arg504 (for the α-structures) and Arg568 and Arg269 (for the *β*-structures). Therefore, a final minimization step was simulated by allowing these three residues to move. Interactions of **8**, **11**, and IP_3 with these active site arginines are shown in Figure 7a−c.

Biological Assay. The ability of compounds to stimulate IP_3 receptors was measured using a low-affinity Ca^{2+} indicator trapped within the intracellular stores of chicken DT 40 cells expressing only recombinant rat type 1 IP_3 receptors as previously.[28]

Acknowledgment. We wish to acknowledge financial support from Ministry of Education, Culture, Sports, Science and Technology, Japan, for Scientific Research 17659027 (to S.S.), the Japan Society for Promotion of Science for Creative Scientific Research 13NP0401 (to A.M.), and the Wellcome Trust for Programme Grants 039662 (to C.W.T.) and 060554 (to B.V.L.P.). We thank Ms. H. Matsumoto, A. Maeda, and S. Oka (Center for Instrumental Analysis, Hokkaido University) for technical assistance with NMR, MS, and elemental analyses and Dr. A. M. Riley for useful discussions.

Supporting Information Available: Analytical data of compounds **13**, **14**, **19**−**21**, **23**, **24**, **26**−**28**, and **33**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Berridge, M. J. Inositol trisphosphate and calcium signaling. *Nature (London)* **1993**, *361*, 315−325.

(2) Wilcox, R. A.; Primrose, W. U.; Nahorski, S. R.; Challiss, R. A. J. New developments in the molecular pharmacology of the *myo*-inositol 1,4,5-trisphosphate receptor. *Trends Pharmacol. Sci*. **1998**, *19*, 467−475.

(3) Potter, B. V. L.; Lampe, D. Chemistry of inositol lipid mediated cellular signaling. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 1933−1972.

(4) (a) Takahashi, M.; Kagasaki, T.; Hosoya, T.; Takahashi, S. Adenophostins A and B: potent agonists of inositol 1,4,5-trisphosphate receptor produced by *Penicillium brevicompactum*. *J. Antibiot.* **1993**, *46*, 1643−1647. (b) Takahashi, M.; Tanzawa, K.; Takahashi, S. Adenophostins, newly discovered metabolites of *Penicillium brevicompactum*, act as potent agonists of the inositol 1,4,5-trisphosphate receptor. *J. Biol. Chem*. **1994**, *269*, 369−372. (c) Hirota, J.; Michikawa, T.; Miyawaki, A.; Takahashi, M.; Tanzawa, K.; Okura, I.; Furuichi, T.; Mikoshiba, K. Adenophostin-mediated quantal Ca^{2+} release in the purified and reconstituted inositol 1,4,5-trisphosphate receptor type 1. *FEBS Lett*. **1995**, *368*, 248−252.

(5) Correa, V.; Nerou, E. P.; Riley, A. M.; Marwood, R. D.; Shuto, S.; Rosenberg, H. J.; Horne, G.; Potter, B. V. L.; Taylor, C. W. Structural determinants of adenophostin A activity at inositol trisphosphate receptors. *Mol. Pharmacol*. **2001**, *59*, 1206−1215 and references therein.

(6) (a) Tatani, K.; Shuto, S.; Ueno, Y.; Matsuda, A. Synthesis of 1-*O*-[(3*S*,4*R*)-3-hydroxytetrahydrofuran-4-yl]-α-D-glucopyranoside 3,4,3′-triphosphate as a novel potent IP_3 receptor ligand. *Tetrahedron Lett.* **1998**, *39*, 5065−5068. (b) Shuto, S.; Tatani, K.; Ueno, Y.; Matsuda, A. Synthesis of adenophostin analogs lacking the adenine moiety as novel potent IP_3 receptor ligands: Some structural requirements for the significant activity of adenophostin A. *J. Org. Chem.* **1998**, *63*, 8815−8824. (c) Kashiwayanagi, M.; Tatani, K.; Shuto, S.; Matsuda, A. Inward current responses to IP_3 and adenophostin-analogues in turtle olfactory sensory neurons. *Eur. J. Neurosci*. **2000**, *12*, 606−612. (d) Abe, H.; Shuto, S.; Matsuda, A. Synthesis of the *C*-glycosidic analog of adenophostin A, a potent IP_3 receptor agonist, using a temporary silicon-tethered radical coupling reaction as the key step. *Tetrahedron* Lett. **2000**, *41*, 2391−2394. (e) Abe, H.; Shuto, S.; Matsuda, A. Synthesis of the *C*-glycosidic analog of adenophostin A and its uracil congener as potential IP_3 receptor ligands. Stereoselective construction of the *C*-glycosidic structure by a temporary silicon-tethered radical coupling reaction. *J. Org. Chem.* **2000**, *65*, 4315−4325. (f) Shuto, S.; Yahiro, Y.; Ichikawa, S.; Matsuda, A. 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. *J. Org. Chem.* **2000**, *65*, 5547−5557. (g) Terauchi, M.; Yahiiro, Y.; Abe, H.; Ichikawa, S.; Stephen, C. Tovey, S. C.; Dedos, S. G.; Taylor, C. W.; Potter, B. V. L.; Matsuda, A.; Shuto, S. Synthesis of 4,8-Anhydro-D-*glycero*-D-*ido*-nonanitol 1,6,7-trisphosphate as a novel IP_3 receptor ligand using a stereoselective radical cyclization reaction based on a conformational restriction strategy. *Tetrahedron* **2005**, *61*, 7865−7873.

(7) (a) Jenkins, A. D. J.; Potter, B. V. L. Synthesis of second messenger mimic related to adenophostin A. *J. Chem. Soc., Chem. Commun.* **1995**, 1169−1170. (b) Marchant, J. S.; Beecroft, M. D.; Riley, A. M.; Jenkins, D. J.; Marwood, R. D.; Taylor, C. W.; Potter, B. V. L. Disacharide polyphosphates based upon adenophostin A activate hepatic D-*myo*-inositol 1,4,5-trisphosphate receptors. *Biochemistry* **1997**, *36*, 6, 12780−12790. (c) Rosenberg, H. J.; Riley, A. M.; Correa, V.; Taylor, C. W.; Potter, B. V. L. *C*-Glycoside based mimics of D-*myo*-inositol 1,4,5-trisphosphate. *Carbohydr. Res*. **2000**, *329*, 7−16. (d) Rosenberg, H. J.; Riley, A. M.; Laude, A. J.; Taylor, C. W.; Potter, B. V. L. Synthesis and Ca^{2+}-mobilizing activity of purine-modified mimics of adenophostin A: a model for the adenophostin-Ins(1,4,5)P_3 receptor interaction. *J. Med. Chem*. **2003**, *46*, 4860−4871 and references therein. (e) Wilcox, R. A.; Erneux, C.; Primrose, W. U.; Gigg, R.; Nahorski, S. R. 2-hydroxyethyl D-glucopyranoside 2,3′,4′-trisphosphate, a novel, metabolically resistant, adenophostin A and *myo*-inositol 1,4,5-trisphosphate analogue potently interacts with the *myo*-inositol 1,4,5-trisphosphate receptor. *Mol. Pharmacol*. **1995**, *47*, 1201−1211. (f) de Kort, M.; Regenbogen, A. D.; Overkleeft, H. S.; Challis, J.; Iwata, Y.; Miyamoto, S.; van der Marel, G. A.; van Boom, J. Synthesis and biological evaluation of cyclophostin: a 5′,6″-tethered analog of adenophostin A. *Tetrahedron* **2000**, *56*, 5915−5928 and references therein. (g) Roussel, F.; Moitessier, N.; Hilly, M.; Chrétien, F.; Mauger, J.-P.; Chapleur, Y. D-*myo*-Inositol-1,4,5-trisphosphate and adenophostin mimics: importance of the spatial orientation of a phosphate group on the biological activity. *Bioorg. Med. Chem*. **2002**, *10*, 759−768 and references therein. (h) Hotoda, H.; Murayama, K.; Miyamoto, S.; Iwata, Y.; Takahashi, M.; Kawase, Y.; Tanzawa, K.; Kaneko, M. Molecular recognition of adenophostin, a very potent Ca^{2+} inducer at the D-*myo*-inositol 1,4,5-trisphosphate receptor. *Biochemistry* **1999**, *38*, 9234−9241.

(8) (a) Postema, M. H. D. Recent developments in the synthesis of *C*-glycosides. *Tetrahedron* **1992**, *48*, 8545−8599. (b) Jaramillo, C.; Knapp S. Synthesis of *C*-aryl glycosides. *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.

(9) (a) Abe, H.; Shuto, S.; Matsuda, A. Highly α- and *β*-selective radical *C*-glycosylation reactions based on the conformational restriction strategy using a controlling anomeric effect. A study on the conformation-anomeric effect-stereoselectivity relationship in the anomeric radical reactions. *J. Am. Chem.* Soc. **2001**, *123*, 11870−11882. (b) Abe, H.; Terauchi, M.; Matsuda, A.; Shuto, S. A study on the conformation-anomeric effect-stereoselectivity relationship in anomeric radical reactions using conformationally restricted glucose derivatives as substrates. *J. Org. Chem*. **2003**, *68*, 7439−7447 and references therein.

(10) Stork, G.; Suh, H. S.; Kim, G. The temporary silicon connection method in the control of regio- and stereochemistry. Applications to radical-mediated reactions. The stereospecific synthesis of *C*-glycosides. *J. Am. Chem. Soc*. **1991**, *113*, 7054−7055.

(11) Radical reactions with a vinylsilyl group as a tether: (a) Shuto, S.; Kanazaki, M.; Ichikawa, S.; Matsuda, A. A novel ring-enlargement reaction of (3-oxa-2-silacyclopentyl)methyl radicals into 4-oxa-3-silacyclohexyl radicals. Stereoselective introduction of a hydroxyethyl group via unusual 6-*endo*-cyclization products derived from 3-oxa-4-silahexenyl radicals, and its application to the synthesis of a 4′α-branched nucleoside. *J. Org. Chem.* **1997**, *62*, 5676−5677. (b) Shuto, S.; Kanazaki, M.; Ichikawa, S.; Minakawa, N.; Matsuda, A. Stereo- and regioselective introduction of 1- or 2-hydroxyethyl group via intramolecular radical cyclization reaction with a novel silicon-containing tether. An efficient synthesis of 4′α-branched 2′-deoxyadenosines. *J. Org. Chem.* **1998**, *63*, 746−754. (c) Ueno, Y.; Nagasawa, Y.; Sugimoto, I.; Kojima, N.; Kanazaki, M.; Shuto, S.; Matsuda, A. Synthesis of oligodeoxynucleotides containing 4′-*C*-[2-[*N*-(2-aminoethyl)carbamoyl]oxy]thymidine and their thermal stability and nuclease-resistance properties. *J. Org. Chem.* **1998**, *63*, 1660−1667. (d) Sugimoto, I.; Shuto, S.; Matsuda, A. One-pot method for the stereoselective introduction of a vinyl group via an atom transfer radical cyclization reaction with a diphenylvinylsilyl group as a temporary connecting tether. Synthesis of 4′α-*C*-vinylthymidine, a potent antiviral nucleoside. *J. Org. Chem.* **1999**, *64*, 7153−7157. (e) Yahiro, Y.; Ichikawa, S.; Shuto, S.; Matsuda, A. 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. *Tetrahedron Lett.* **1999**, *40*, 5527−5531. (f) Shuto, S.; Sugimoto, I.; Matsuda, A. Mechanistic study of the ring-enlargement reaction of (3-oxa-2-silacyclopentyl)methyl radicals into 4-oxa-3-silacyclohexyl radicals. Evidence for a pentavalent silicon-bridging radical transition state in 1,2-rearrangement reactions of β-silyl radicals. *J. Am. Chem. Soc.* **2000**, *122*, 1343−1351. (g) Sukeda, M.; Shuto, S.; Sugimoto, I.; Ichikawa, S.; Matsuda, A. Synthesis of pyrimidine 2′-deoxy-ribonucleosides branched at the 2′-position via radical atom-transfer cyclization reaction with a vinylsilyl group as a radical-acceptor tether. *J. Org. Chem.* **2000**, *65*, 8988−8996.

(12) Radical reactions with a allylsilyl group as a tether: (a) Xi, Z.; Agback, P.; Plavec, J.; Sandström, A.; Chattopadhyaya, J. New stereocontrolled synthesis of isomeric *C*-branched-D-nucleosides by intramolecular free-radical cyclization-opening reactions based on temporary silicon connection. *Tetrahedron* **1992**, *48*, 349−370. (b) Kanazaki, M.; Ueno, Y.; Shuto, S.; Matsuda, A. Highly nuclease-resistant phosphodiester-type oligodeoxynucleotides containing 4′α-*C*-aminoalkylthymidines form thermally stable duplexes with DNA and RNA. A candidate for potent antisense molecules. *J. Am. Chem. Soc.* **2000**, *122*, 2422−2432.

(13) **13**, $J_{2,3}$ = 4.2 Hz; **14**, $J_{2,3}$ = 2.0 Hz, $J_{3,4}$ = ca. 0 Hz. See also a preliminary account on the synthesis of β-*C*-glucosides by radical cyclization based on the conformational restriction strategy: Terauchi, M.; Matsuda, A.; Shuto, S. Efficient synthesis of β-*C*-glucosides via radical cyclization with a silicon tether based on the conformational restriction strategy. *Tetrahedron Lett.* **2005**, *46*, 6555−6558.

(14) (a) Tius, A. M.; Bushe-Petersen, J. Stereochemical control in the oxymercuration of 5-alken-1-ols. *Tetrahedron Lett.* **1994**, *35*, 5181−5184. (b) Hosoya, T.; Ohashi, Y.; Matsumoto, T.; Suzuki, K. On the stereochemistry of aryl *C*-glycosides: unusual behavior of bis-TBDPS protected aryl *C*-olivosides. *Tetrahedron Lett.* **1996**, *37*, 663−666. (c) Walford, C.; Jackson, R. F. W.; Rees, N. H.; Clegg, W.; Heath, S. L. Reaction of thiophenol with glucal epoxides: X-ray structure of 3,4,6-tri-*O*-*tert*-butyldimethylsilyl-1-*S*-phenyl-1-thio-D-glucopyranoside. *Chem. Commun.* **1997**, 1855−1856. (d) Ichikawa, S.; Shuto, S.; Matsuda, A. The first synthesis of herbicidin B. Stereoselective construction of the tricyclic undecose moiety by conformational restriction strategy using steric repulsion between adjacent bulky silyl protecting groups on a pyranose ring. *J. Am. Chem. Soc.* **1999**, *121*, 10270−10280. (e) Abe, H.; Shuto, S.; Tamura, S.; Matsuda, A. An efficient method for preparing fully *O*-silylated pyranoses conformationally restricted in the unusual $^1C_4$-form. *Tetrahedron Lett.* **2001**, *42*, 6159−6161.

(15) Fleming, I.; Henning, R.; Plaut, H. The phenydimethylsilyl group as a masked form of the hydroxy group. *J. Chem. Soc., Chem. Commun.* **1984**, 29−31.

(16) Watanabe, Y.; Komoda, Y.; Ebisuya, K.; Ozaki, S. An efficient phosphorylation method using a new phosphitylating agent, 2-diethylamino-1,3,2-benzodioxaphosphepane. *Tetrahedron Lett.* **1990**, *31*, 255−256.

(17) (a) Lewis, M. D.; Cha, J. K.; Kishi, Y. Highly stereoselective approaches to alpha- and beta-*C*-glycopyranosides. *J. Am. Chem. Soc.* **1982**, *104*, 4976−4978. (b) Wang, Y.; Babirad, S. A.; Kishi, Y. Preferred conformation of C-glycosides. 8. Synthesis of 1,4-linked carbon disaccharides. *J. Org. Chem.* **1992**, *57*, 468−481. (c) Minehan, T. G.; Kishi, Y. β-Selective *C*-glycosidations: Lewis-acid mediated reactions of carbohydrates with silyl ketene acetals. *Tetrahedron Lett.* **1997**, *38*, 6815−6818. (d) Reference 8d, pp 57−60.

(18) Tamura, S.; Abe, H.; Matsuda, A.; Shuto, S. Control of the α/β-stereoselectivity in Lewis acid-promoted *C*-glycosidation using a controlling anomeric effect based on the conformational restriction strategy. *Angew. Chem.* **2003**, *42*, 1021−1023.

(19) (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983; pp 209−221. (b) Juaristi, E.; Cuevas, G. Recent studies of the anomeric effect. *Tetrahedron* **1992**, *48*, 5019−5087 (c) Thatcher, G. R. J. Ed. *The Anomeric Effect and Associated Stereoelectronic Effects*; ACS Symposium Series 539; American Chemical Society: Washington, DC, 1993. (d) Juaristi, E.; Cuevas, G. *The Anomiric Effect*; CRC Press: Boca Raton, 1995. (e) Thibaudeau, C.; Chattopadhyaya, J. *Stereoelectronic Effects in Nucleosides and Nucleotides and their Structural Implication*; Uppsala University Press: Uppsala, 1999.

(20) (a) Pothier, N.; Goldstein, S.; Deslongchamps, P. Cyclization of hydroxyenol ethers into spiroacetals. Evidence for the position of the transition state and its implication on the stereoelectronic effects in acetal formation. *Helv. Chim. Acta* **1992**, *75*, 604−620. (b) Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. Stereochemical reversal of nucleophilic substitution reactions depending upon substituent: reactions of heteroatom-substituted six-membered-ring oxocarbenium ions through pseudoaxial conformers. *J. Am. Chem. Soc.* **2000**, *122*, 168−189.

(21) Terauchi, M.; Abe, H.; Matsuda, A.; Shuto, S. An efficient synthesis of β-*C*-glycosides based on the conformational restriction strategy: Lewis acid-promoted silane reduction of the anomeric position with complete stereoselectivity. *Org. Lett.* **2004**, *6*, 3751−3754.

(22) (a) Montchamp, J.-L.; Tian, F.; Hart, M. E.; Frost, J. W. Butane 2,3-bisacetal protection of vicinal diequatorial diols. *J. Org. Chem.* **1996**, *61*, 3897−3899. (b) Hense, A.; Ley, S. V.; Osborn, H. M. I.; Owen, D. R.; Poisson, J.-F.; Warriner, S. L.; Wesson, K. E. Direct preparation of diacetals from 1,2-diketones and their use as 1,2-diol protecting groups. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2023−2032.

(23) de Kort, M.; Regenbogen, A. D.; Valentijn, A. R. P. M.; Challiss, R. A. J.; Iwata, Y.; Miyamoto, S.; van der Marel, G. A.; van Boom, J. H. Spirophostins: Conformationally restricted analogues of adenophostin A. *Chem. Eur. J.* **2000**, *6*, 2696−2704.

(24) Mignery, G. A.; Newton, C. L,; Archer, B. T.; Südhof, T. C. Structure and expression of the rat inositol 1,4,5-trisphosphate receptor. *J. Biol. Chem.* **1990**, *265*, 12679−12685.

(25) Miyazaki, J.; Takaki, S.; Araki, K.; Tashiro, F.; Tominaga, A.; Takatsu, K.; Yamamura, K. Expression vector system based on the chicken β-actin promoter directs efficient production of interleukin-5. *Gene* **1989**, *79*, 269−277.

(26) Sugawara, H.; Kurosaki, M.; Takata, M.; Kurosaki, T. Genetic evidence for involvement of type 1, type 2 and type 3 inositol 1,4,5-trisphosphate receptors in signal transduction through the B-cell antigen. *EMBO J.* **1997**, *16*, 3078−3088.

(27) Cardy, T. J.; Traynor, D.; Taylor, C. W. Differential regulation of types-1 and -3 inositol trisphosphate receptors by cytosolic Ca^{2+}. *Biochem. J.* **1997**, *328*, 785−793.

(28) Laude, A. J.; Tovey, S. C.; Dedos, S. G.; Potter, B. V. L.; Lummis, S. C. R.; Taylor, C. W. Rapid functional assays of recombinant IP_3 receptors. *Cell Calcium* **2005**, *38*, 45−51.

JM051039N