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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

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Abstract—4,8-Anhydro-D-*glycero*-D-*ido*-nonanitol 1,6,7-trisphosphate (**9**), designed as a novel IP_3 receptor ligand having an α-*C*-glycosidic structure, was synthesized via a radical cyclization reaction with a temporary connecting allylsilyl group as the key-step. Phenyl 2-*O*-allyldimethylsilyl-3,4-bis-*O*-TBS-1-seleno-β-D-glucopyranoside (**10a**), conformationally restricted in the unusual $^1C_4$-conformation, was treated with Bu_3SnH/AIBN to form the desired α-cyclization product **16a** almost quantitatively. On the other hand, when a conformationally unrestricted *O*-benzyl-protected 2-*O*-allyldimethylsilyl -1-selenoglucoside **15** was used as the substrate, the radical reaction was not stereoselective and gave a mixture of the α-and β-products. From **16a**, the target *C*-glucoside trisphosphate **9** was synthesized via phosphorylation of the hydroxyls by the phosphoramidite method. During the synthetic study, an efficient procedure for the oxidative C–Si bond cleavage, via a nucleophilic substitution at the silicon with *p*-MeOPhLi followed by Fleming oxidation, was developed. The *C*-glycoside **9** was found to be a full agonist for Ca^{2+} mobilization, although its activity was weaker than that of the natural ligand IP_3. Thus, the α-*C*-glucosidic structure was shown to be a useful mimic of the *myo*-inositol backbone of IP_3.
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1. Introduction

D-*Myo*-inositol 1,4,5-trisphosphate (IP_3, **1**, Fig. 1)[1] is a biologically important intracellular Ca^{2+}-mobilizing second messenger whose analogues have been extensively synthesized for the development of specific ligands for IP_3 receptors. These ligands have been shown to be effective in investigating the mechanism of IP_3-mediated Ca^{2+} signaling pathways. They may also be useful as leads for the development of potentially beneficial drugs.[2,3]

Adenophostin A (**2**), isolated from *Penicillium brevicompactum*, is a very potent IP_3 receptor agonist,[4] and several groups, including ours, have been performing synthetic studies of novel IP_3 receptor ligands based on its structure.[5–7] 2-Hydroxyethyl α-D-glucopyranoside 3,4,2′-trisphosphate (**4**) was originally designed and synthesized as a highly simplified analogue of adenophostin A, and was demonstrated to be an agonist of the IP_3 receptor.[5,7a,b,l] These studies indicated that the α-D-glucopyranoside structure is a good bioisostere of the *myo*-inositol backbone of IP_3 and that the three-dimensional positioning of the three phosphate moieties and, in particular, the lone 'auxiliary' phosphate group, is significant to affect the activity.[5,6b] It has also been shown that the adenine moiety of adenophostin A can be replaced by other aromatic rings as a bioisostere; e.g. the uracil congener **5** *inter alia* has a strong Ca^{2+}-mobilizing activity close to that of adenophostin A (Fig. 1).[5,7k]

We are interested in *C*-glycosidic analogues having the α-D-glucopyranoside structure as potential IP_3 receptor ligands, since *C*-glycosides are known to be biologically stable mimics of the corresponding *O*-glycosides.[8] Thus, we have synthesized the *C*-glycosidic analogue **3** of adenophostin A and also its uracil congener **6**,[6d,e] which proved to be very potent IP_3-receptor agonists.[9] The α-*C*-glucoside

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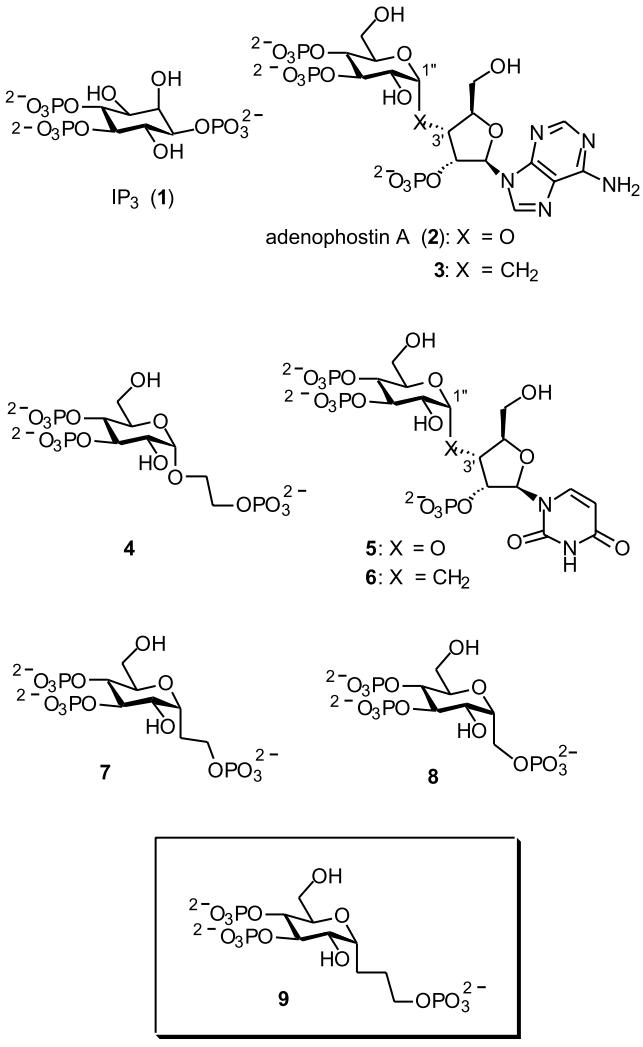


Figure 1. IP_3 receptor ligands.

trisphosphate **7**, having a C2-chain at the anomeric position, was also designed and synthesized as a simplified *C*-gycosidic IP_3 receptor ligand, the binding affinity of which was only about 2-fold lower than that of IP_3 itself.[6f] Interestingly, the *O*-glucoside trisphosphate **4**, having a structure similar to the *C*-glycoside **7**, was 25-fold lower than IP_3 in its affinity for the receptor.[5,7a,b,l] The significantly different activity between the *C*-glycoside **7** and the *O*-glycoside **4** may be due to the relative properties of the *O*- and the *C*-glycosidic linkage.[10] A second explanation for the difference may be due to the longer side-chain length of **4** compared with that of **7**, since the three-dimensional location of the phosphate groups of IP_3 receptor ligands seems to be a critical factor for their biological activity[3,5] Another shorter chain, C1-type α-*C*-glucoside trisphosphate **8**, was also synthesized; however, its Ca^{2+}-mobilizing activity was about 17-fold lower than IP_3,[7h] suggesting that the anomeric C1-unit might be too short for the effective binding of the molecule to the receptor. On the basis of these findings, we decided to synthesize another α-*C*-glucoside trisphosphate, i.e. 4,8-anhydro-D-*glycero*-D-*ido*-nonanitol 1,6,7-trisphosphate (**9**), whose anomeric C3-side-chain length is similar to that of **4**, in order to further clarify the structure–activity relationship of these *C*-and *O*-glucoside trisphosphates.

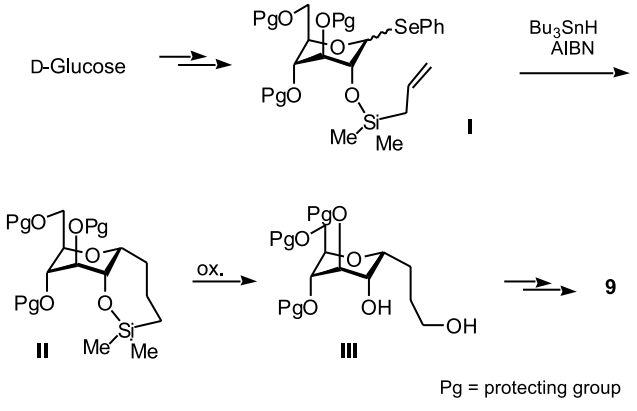
2. Result and discussion

2.1. Synthetic plan

Due to their unique biological activities, considerable effort has been devoted to the development of useful methods for the preparation of *C*-glycosides.[8,11] The use of radical reactions is one of the most efficient methods for constructing *C*-glycosidic bonds; therefore we have been working on the development of stereoselective intramolecular and intermolecular radical *C*-glycosidation reactions.[6d-f,11c,d]

The allylsilyl group was originally used as a very effective radical acceptor tether for the stereoselective introduction of a C_3 unit by Chattopadohyaya and co-workers.[12a] A branched thymidine derivative having an aminopropyl group at the 4′-posistion, which proved to be an effective nucleoside unit in antisense studies, was synthesized using the radical reaction with this tether as the key step.[12b] We planned to develop a procedure for introducing a C3 unit stereoselectively at the anomeric α-position of D-glucose via the radical cyclization reaction with the allylsilyl group as a temporary connecting tether[13] and apply it to the synthesis of the target *C*-glycoside trisphosphate **9**.

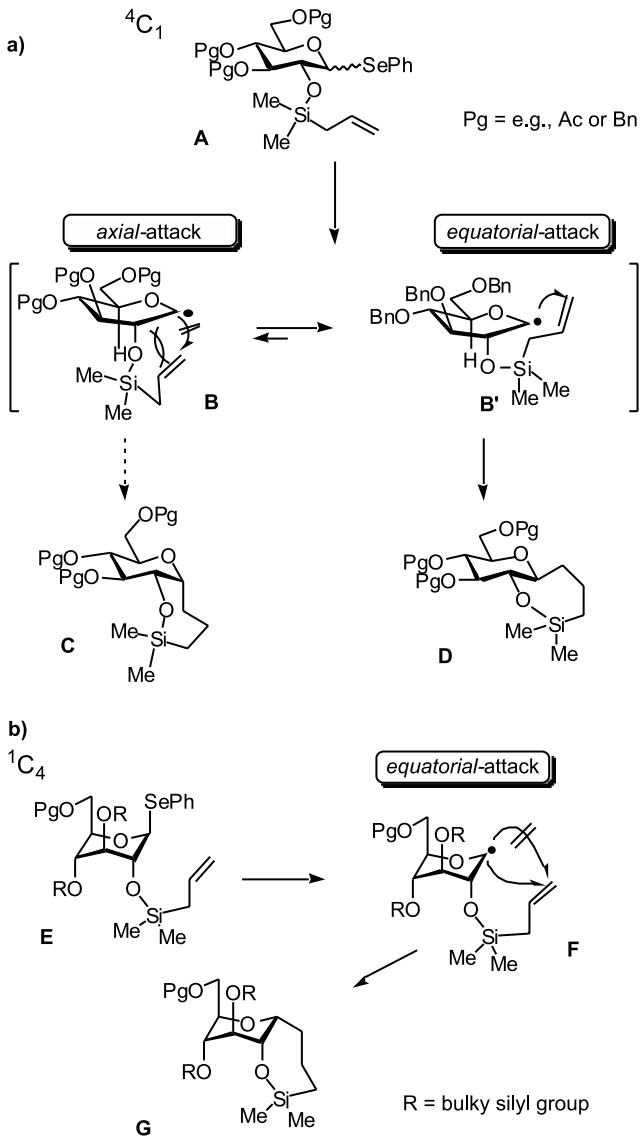
Scheme 1 shows our synthetic plan. We chose the phenyl 1-seleno-D-glucopyranoside **I** with an allylsilyl group at the 2-hydroxyl as the substrate for the radical reaction, because it seemed to be stable and easy to prepare. The radical cyclization reaction of **I** under reductive conditions gives the 7-endo *cis*-cyclized product **II**. Subsequent oxidative cleavage of the C–Si bond would give the desired α-*C*-glycoside **III**, which could then be converted into the target trisphosphate **9** via introduction of the three phosphate groups using the phosphoramidite method.



Scheme 1.

In this synthetic plan, the key would be whether the radical cyclization occurred stereoselectively to form the desired α-product. The stereoselectivity of the radical cyclization is significantly influenced by the conformation of the substrates.[14] Giese and co-workers previously clarified the

conformation of the anomeric radical intermediate produced from a tetra-*O*-acetyl-protected glucose derivative using ESR spectroscopy:[15] the glucosyl radical assuming a $B_{2,5}$-boat-like conformation is maximally stabilized in the conformation due to an effective interaction of the radical orbital (SOMO) with the σ^*-orbital of the adjacent C_2–O_2 bond and also with the p-orbital of a lone pair of the ring oxygen in their periplanar arrangement. Accordingly, as shown in Scheme 2, the anomeric radical, derived from the 2-*O*-allylsilyl substrate **A** assuming a usual $^4C_1$-chair conformation, would prefer such a $B_{2,5}$-boat-like conformation **B** (**B′**). Approach of the tether terminal to the anomeric position from the α-axial direction forming **C** might be disfavored because of the significant 1,2- and 1,5-steric repulsion (**B**) due to the axial orientation of the 2-*O*-silyl and the 5-H substituents, and consequently cyclization via the β-equatorial-attack (**B′**) might preferentially occur to result in the formation of *trans*-cyclized product **D**.



Scheme 2.

Based on these considerations, we designed substrate **E** for the radical reaction, the conformation of which should be restricted to an unusual $^1C_4$-chair form. We recently demonstrated by ab initio calculations that the anomeric radical intermediate preferentially assumes the substrate-like $^1C_4$-form when the conformation of the precursors of the radical is restricted in an unusual $^1C_4$-chair form.[11d] Hence we expected that the radical cyclization using the conformationally $^1C_4$-restricted substrate **E** would give stereoselectively the desired α-cyclization product **G**, via $^1C_4$-chair-like anomeric radical intermediate **F**, where 1,2-*trans*-cyclization would be sterically impossible because of the axial orientation of the 2′-tether, as shown in Scheme 2b.[16] The conformational restriction of the substrate to the desired $^1C_4$-form was thought to be possible by employing the significantly bulky silyl protecting groups as described bellow.

2.2. Design and preparation of the conformationally flipped 3,4-*O*-silyl substrates

Based on the above considerations, the 3,4-bis-*O*-silyl-protected substrates **10a**, **10b**, and **10c**, were designed for the radical reaction (Fig. 2). It is known that introducing a significantly bulky protecting group at the 3,4-*trans*-hydroxyl groups of pyranoses causes a flip of their conformation leading to a $^1C_4$-form, in which the bulky substituents are in axial positions due to mutual steric repulsion.[11b–e,17–20] Accordingly, the 3,4-*O*-silyl substrates **10a–c** would assume an unusual $^1C_4$-conformation due to the significant steric repulsion between the bulky silyl groups.

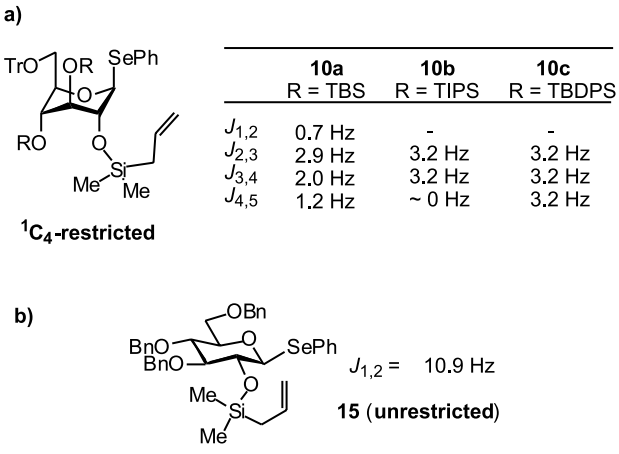
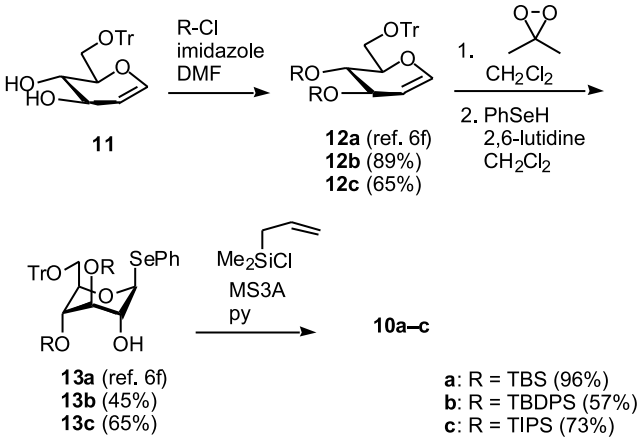


Figure 2. Conformationally restricted (a) and unrestricted (b) substrates of the radical cyclization reaction.

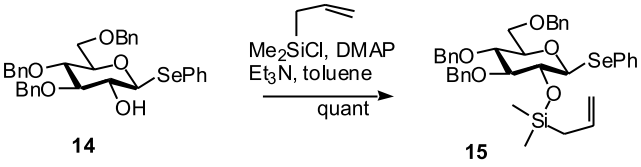
On the other hand, there was concern that the radical reaction might not be initiated if the silyl group was too bulky, since attack of the tin radical at the anomeric selenium might be prevented due to significant steric hindrance. In fact, we have experienced such decrease in reactivity at the anomeric position due to the extreme steric hindrance by bulky silyl groups in $^1C_4$-restricted substrates.[11c,d] Therefore, we planned to examine three $^1C_4$-restricted substrates **10a**, **10b**, and **10c**, with different silyl protecting groups as the radical reaction substrates.

The substrates **10a–c** were prepared from the known glucal **11**[21] as shown in Scheme 3. TBS, TBDPS, or TIPS groups were introduced at the 3,4-*trans*-hydroxyls of **11** by the usual method to give **12a–c**, respectively. The TBS-protected glucal **12a** was successively treated with dimethyldioxirane and with PhSeH/Et_3N in CH_2Cl_2 to give 1-β-phenylselenide **13a** along with the corresponding α-anomer. When 2,6-lutidine was used instead of Et_3N as a base in the phenylselenation step, the β-phenylselenide **13a** was obtained as the sole product. Similarly, β-phenylselenides **13b** and **13c** were stereoselectively prepared. An allyldimethylsilyl group was then introduced at the 2-hydroxyl of the anomeric phenylselenides **13a–c** to provide the radical reaction substrates **10a–c**.



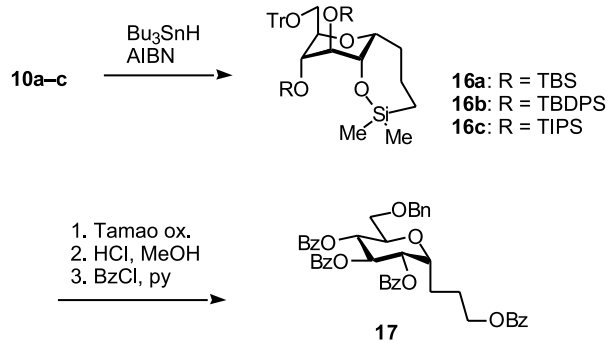
Scheme 3.

We also prepared a conformationally unrestricted substrate **15**, i.e. the 2-*O*-allyldimethylsilyl ether of phenyl 3,4,6-tri-*O*-benzyl-1-seleno-β-D-glucose (Fig. 2b) to clarify whether the conformational restriction of the substrate in the $^1C_4$-form was in fact essential for the α-selective radical cyclization. Phenyl 3,4,6-tri-*O*-benzyl-1-seleno-β-D-glucose (**14**)[22] was treated with allyldimethylchlorosilane, DMAP, and Et_3N in toluene at room temperature to give quantitatively the corresponding 2-*O*-silyl ether **15** (Scheme 4).



Scheme 4.

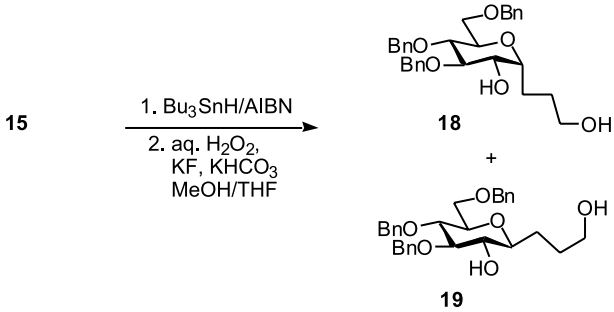
The conformation of the substrates **10a–c** and **15** was investigated by ^1H NMR (Fig. 2). The unrestricted substrate **15** has large coupling constants (ca. 10 Hz) between the ring protons showing its $^4C_1$-chair-like conformation. On the other hand, considerably smaller coupling constants (0–3.2 Hz) in the 3,4-*O*-silyl-protected substrates **10a–c** indicate their preference for the flipped $^1C_4$-conformation, as expected.



Scheme 5.

2.3. Radical reaction of the conformationally restricted and unrestricted substrates

The radical reactions of the $^1C_4$-restricted substrates **10a–c** and also the unrestricted substrate **15** were performed by slow addition of a mixture of Bu_3SnH and AIBN to a refluxing solution of the substrate in benzene (80 °C), toluene (110 °C), or *t*-butylbenzene (130 °C) (Schemes 5 and 6). The results are summarized in Table 1. First, the reaction was examined by slow addition of 2 equiv of Bu_3SnH and 0.67 equiv of AIBN to the 0.005 M solution of the bis-*O*-TBS substrate **10a** in benzene. However, the radical reaction was not initiated under the conditions, and substrate **10a** was completely recovered (entry 1). This suggests that the bulky silyl groups hindered the approach of the tin radical to the anomeric selenium, as indicated above. When **10a** was treated with 2.0 equiv of Bu_3SnH under higher substrate concentration conditions (0.05 M), the radical reaction occurred to produce the desired α-*C*-glucoside **16a** almost quantitatively (entry 2), the structure of which was confirmed after its conversion into the corresponding penta-*O*-benzoate **17**, by successive treatment under Tamao oxidation conditions,[23] HCl/MeOH, and BzCl/pyridine (Scheme 5). The corresponding α-cyclized products **16b** and **16c** were also exclusively obtained in high yield by the radical reactions (entries 3 and 4), when the other two $^1C_4$-restricted substrates, TBDPS-protected **10b** and TIPS-protected **10c**, were treated under identical conditions as for those of entry 2 for **10a**.



Scheme 6.

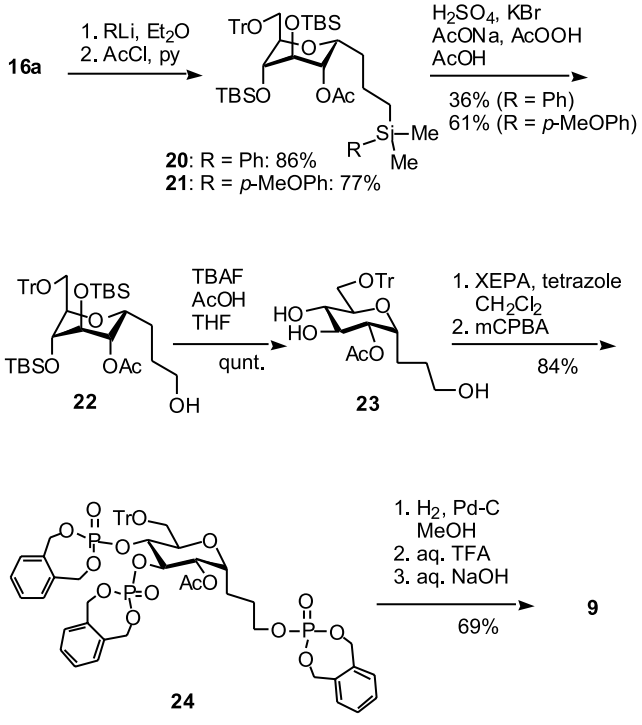
We next examined the radical cyclization with the conformationally unrestricted tri-*O*-benzyl substrate **15** by a similar procedure with Bu_3SnH and AIBN, followed by the Tamao oxidation (Scheme 6). First, the reaction was carried out in benzene under reflux under conditions

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

Entry	Substrate (concn, M)	Solvent	Temp (°C)	Product	Yield (%)	α/β ratio
1	**10a** (0.005)	Benzene	80	No reaction	—	—
2	**10a** (0.05)	Benzene	80	**16a**	97[b]	Only α
3	**10b** (0.05)	Benzene	80	**16b**	85	Only α
4	**10c** (0.05)	Benzene	80	**16c**	84	Only α
5	**15** (0.005)	Benzene	80	**18**, **19**	73	1:2.9[c]
6	**15** (0.005)	Toluene	110	**18**, **19**	80	1:4.1[c]
7	**15** (0.005)	*t*-BuPhH	130	**18**, **19**	62	1:3.1[c]

[a] To a heating solution of the substrate in benzene, toluene, or *t*-BuPhH, a mixture of Bu_3SnH (entries 1, 5–7, 1.3 equiv; entries 2–4, 2 equiv;) and AIBN (0.67 equiv) in the same solvent was added slowly (entries 1, 5–7, over 4 h; entries 2–4, over 2 h).
[b] Mean value of three experiments.
[c] After treatment of a mixture of the radical reaction products under Tamao oxidation conditions, the α/β ration was determined by HPLC.

identical to those of entry 1 for **10a**. The radical reaction took place in spite of the lower concentration of the substrate (0.005 M) to give, after the Tamao oxidation, a mixture of the α-*C*-glucoside **18** and the β-*C*-glucoside **19** (entry 5: yield 73%). After isolation of the both anomers, ^{1}H NMR analyses proved that the major product was not the α-anomer **18** but the β-anomer **19** ($\alpha/\beta=1:2.9$). When the reaction was performed at 110 °C in toluene, the β-selectivity was further increased (entry 6: yield 80%, $\alpha:\beta=1:4.1$). At further higher temperature, the yield and the β-stereoselectivity decreased (entry 7). Therefore, the desired α-*C*-glycoside **18** was not obtained as the major product via the radical reaction of the unrestricted tri-*O*-benzyl substrate **15**. However, it should be noted that the reaction with the substrate **15** gave the *trans*-cyclized β-*C*-glycoside as the major product, since intermolecular anomeric radical reactions of glucose derivatives have been demonstrated to produce the corresponding α-product selectively probably because of the anomeric effect.



Scheme 7.

These results clearly indicate that the conformational restriction strategy is highly effective for realizing stereoselective radical cyclization at the anomeric position.

2.4. Synthesis of the target *C*-glucoside trisphosphate via the novel C–Si bond fission

The 3,4-*O*-TBS-protected radical reaction product **16a**, the overall yield of which was the highest among the series, was used for further derivatization, as shown in Scheme 7. To convert **16a** into the target *C*-glucoside trisphosphate **9**, oxidative C–Si bond fission in **16a** was required without cleaving the 3,4-*O*-TBS groups. The usual Tamao oxidation conditions, including use of the fluoride ion, would likely remove the silyl protecting groups, at least to some extent. Consequently, **16a** was exposed to conditions with H_2O_2/$KHCO_3$/KBr in aqueous MeOH/THF at room temperature. Although, the desired C–Si bond fission occurred selectively under these conditions, the reaction was extremely slow to require one month of stirring. Furthermore, the reaction was not reproducible. Thus, an alternative method was sought.

It is known that aromatic carbon–Si bonds are much more readily cleaved via an electrophilic substitution at the silicon center than aliphatic ones;[24] therefore, the arylsilyl groups could be a useful latent hydroxy group. Thus, **16a** was treated with PhLi in Et_2O at −78 °C followed by acetylation of the 2-hydroxyl to produce, in 86% yield, the ring-opened derivative **20** having a Ph–Si bond (Scheme 7). Although Fleming oxidation of **20** was examined under various conditions, detritylation was unavoidable under these conditions and resulted in a lower yield of the desired primary alcohol **22**.

Considerable acidic conditions are required for the Fleming oxidation, because *ipso*-protonation is essential to proceed the oxidation.[24] We speculated that if an electron-donating substituent were attached at the *ortho*- or *para*-position of the phenyl moiety, the *ipso*-protonation could effectively took place even under mild acidic conditions so that the oxidation would progress without removal of the trityl group. Thus, another ring-opening intermediate **21** having a *p*-MeOPhSi group was prepared by treating **16a** with *p*-MeOPhLi in THF followed by acetylation. When **21** was treated under Fleming oxidation conditions with AcOOH/AcOH/AcONa/H_2SO_4/KBr,[25] the desired primary alcohol **22** was successfully obtained in 61% yield, as expected.

The two *O*-silyl groups of **22** were simultaneously removed with TBAF in the presence of AcOH to give **23**. Using the phosphoramidite method with *o*-xylene *N*,*N*-diethylphosphoramidite (XEPA) developed by Watanabe and co-workers,[26] the phosphate units were next introduced. Thus, **23** was treated with XEPA and tetrazole in CH_2Cl_2, followed by oxidation with *m*-CPBA to give the desired trisphosphate derivative **24** in 84% yield. Finally, the *o*-xylene, trityl, and acetyl protecting groups were successively removed by hydrogenation, acidic hydrolysis, and basic hydrolysis to furnish the target **9** in 69% yield as the sodium salt, after treatment with ion-exchange resin.

As described above, we have synthesized the *C*-glucosidic trisphosphate **9** via the radical cyclization reaction using the conformationally restricted substrate as the key step. During the study, we also developed an efficient procedure for oxidative C–Si bond cleavage via nucleophilic substitution at the silicon atom with *p*-MeOPhLi. There has been growing interest in the use of silicon-containing tethers for intramolecular radical cyclization reactions, which are very useful for the regio- and stereoselective introduction of a carbon substituent based on a temporary silicon connection.[27] One drawback of this kind of temporary silicon-connecting radical reaction methods is that silyl protecting groups, which may be the most versatile protecting groups in recent organic chemistry, do not survive the subsequent oxidative Si–C bond cleavage step under normal Tamao oxidation conditions. As a result, the two-step method described here, i.e. the nucleophilic ring-opening with *p*-MeOPhLi followed by Fleming oxidation, could be of significant utility.

2.5. Biological effects

The ability of synthesized **9** to stimulate opening of the pore of recombinant rat type 1 IP_3 receptors expressed in chicken B cells that otherwise lack IP_3 receptors was measured using a fluorescent Ca^{2+} indicator trapped within the lumen of the intracellular Ca^{2+} store.[28–31] The results are shown in Table 2 and are presented as relative potency to those obtained using both IP_3 (**1**) and adenophostin A (**2**). The *C*-glycoside **9** having a C3-chain was found to be a full agonist for Ca^{2+} mobilization with a potency about 8-fold lower than that of IP_3. The activity of **9** seems to be somewhat stronger than **8** having a C1-chain, which was about 16-fold less potent than IP_3.[5,7i] By contrast, the binding affinity of **7**, having a C2-chain, for IP_3 receptors was shown to be only about 2-fold lower than that of IP_3 itself.[6f] These results clearly show that *C*-glycoside chain length can have a marked effect upon biological activity with an optimum chain length of C2 in this series. All of the compounds studied were clearly significantly weaker than adenophostin A.

Thus, the three-dimensional positioning of the three phosphate moieties and, in particular, that of the lone 'auxiliary' phosphate group, was effectively investigated, and the *myo*-inositol backbone of IP_3 was shown to be replaced by the α-D-*C*-glucosidic structure. It should be noted that this strategy, employing a series of *C*-glycosides as stable mimics of the *O*-glycoside, is essential because the corresponding *O*-glycoside trisphosphates, e.g. **25** and **26** (Fig. 3), could not be provided due to their predictable instability due to the O–C–O–O–P (**25**) or O–C–O–C–O–P (**26**) structure. Full details of *C*-glycoside based IP_3 analogue structure–activity relationships will appear elsewhere.

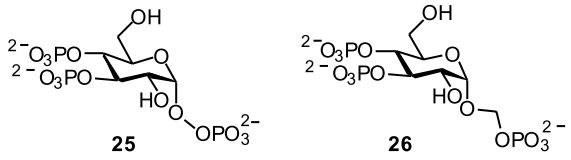


Figure 3. Putatively unstable α-*O*-glucoside trisphosphates.

3. Experimental

3.1. General methods

Chemical shifts are reported in ppm downfield from tetramethylsilane (^1H and ^{13}C) or H_3PO_4 (^{31}P), and *J* values are given in hertz. The ^1H 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 7734 or 9385. Reactions were carried out under an argon atmosphere.

3.1.1. (2*R*,3*R*,4*R*)-3,4-Bis-(*tert*-butyldiphenylsilyloxy)-3,4-dihydro-2-(triphenylmethoxymethyl)-2*H*-pyran (12b). A mixture of **11**[21] (1.94 g, 5 mmol), TBDPSCl (3.90 mL, 15 mmol) and imidazole (20.0 g, 30 mmol) in DMF (40 mL) was stirred at 60 °C for 20 h. The resulting 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, 20–33% benzene in hexane) to give **12b** (3.90 g, 89%) as a white solid: ^1H NMR (400 MHz, $CDCl_3$) δ 7.53–7.13 (m, 35H), 6.39 (d, 1H, *J*=6.2 Hz), 4.45 (m, 1H), 4.24 (m, 1H), 3.84 (dd, 1H, *J*=8.7, 10.8 Hz), 3.81 (s, 1H), 3.18 (d, 1H, *J*=5.0 Hz), 2.97 (dd, 1H, *J*=2.6, 10.8 Hz), 0.89 (s, 9H), 0.71 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 142.7, 135.5, 135.5, 135.4, 135.4, 133.7, 133.4, 133.2, 129.5, 129.5, 129.4, 129.4, 129.3, 128.6, 127.5, 127.5, 127.4, 127.2, 126.6, 100.3, 86.4, 78.1, 70.8, 64.7, 62.3, 26.9, 26.8, 19.3, 19.0; LRMS (FAB, positive) *m/z* 887 (MNa^+). Anal. Calcd for $C_{57}H_{60}O_4Si_2$: C, 79.12; H, 6.99. Found: C, 79.16; H, 7.17.

Table 2. Ca^{2+} release by rat type 1 IP_3 receptors expressed in DT40 cells

Compound	EC_{50}, nM	Hill slope	Ca^{2+} release, %	*n*	Relative potency	
					IP_3	Adenophostin A
IP_3 (**1**)	24.8±2.1	1.21±0.06	78±2	11	1	0.087±0.009
Adenophostin A (**2**)	2.1±0.2	1.54±0.13	76±1	12	12.77±4.46	1
9	213±37	1.39±0.27	69±2	5	0.12±0.01	0.009±0.001

3.1.2. (2*R*,3*R*,4*R*)-3,4-Bis-(triisopropylsilyloxy)-3,4-dihydro-2-(triphenylmethoxymethyl)-2*H*-pyran (12c). Compound **12c** (2.30 g, 65%) was obtained as a colorless oil from **11** (1.94 g, 5.0 mmol) as described above for the synthesis of **12b**, after purification by column chromatography (SiO_2, 20–33% benzene in hexane): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, 6H, J=7.1 Hz), 7.44–7.15 (m, 9H), 6.36 (d, 1H, J=6.3 Hz), 4.72 (m, 1H), 4.30 (m, 1H), 3.81–3.74 (m, 3H), 3.07 (dd, 1H, J=2.4, 11.1 Hz), 1.01 (m, 21H), 0.87 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 142.5, 128.6, 127.5, 126.6, 100.4, 86.5, 78.7, 70.6, 64.8, 62.4, 18.2, 18.6, 18.1, 12.6, 12.4; LRMS (FAB, positive) m/z 723 (MNa^+). Anal. Calcd for $C_{43}H_{64}O_4Si_2$: C, 73.66; H, 9.20. Found: C, 73.45; H, 9.25.

3.1.3. Phenyl 3,4-Bis-*O*-*tert*-butyldiphenylsilyl-6-*O*-triphenylmethyl-1-seleno-β-D-glucopyranoside (13b). A mixture of **12b** (864 mg, 1.0 mmol) and dimethyldioxilane (ca. 0.1 M in acetone, 14 mL, ca. 1.4 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 1 h and then dried (Na_2SO_4) and evaporated. A mixture of the residue, PhSeH (128 μL, 1.2 mmol) and 2,6-lutidine (800 μL, 6.9 mmol) in CH_2Cl_2 (5 mL) was stirred at 0 °C for 12 h and then evaporated. The residue 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, 0–1% AcOEt in hexane) to give **13b** (467 mg, 45%) as a white foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–6.99 (m, 40H), 5.47 (d, 1H, J=5.0 Hz), 4.09 (dd, 1H, J=4.8, 7.2 Hz), 3.94 (brs, 1H), 3.78 (m, 1H), 3.75 (dd, 1H, J=7.2, 9.9 Hz), 3.65 (d, 1H, J=2.9 Hz), 3.04 (d, 1H, J=9.1 Hz), 2.89 (dd, 1H, J=4.7, 9.9 Hz), 0.87 (s, 9H), 0.72 (s, 9H); HRMS calcd $C_{63}H_{66}NaO_5SeSi_2$: 1061.3521 (MNa^+), found 1061.3510.

3.1.4. Phenyl 3,4-bis-*O*-triisopropylsilyl-6-*O*-triphenylmethyl-1-seleno-β-D-glucopyranoside (13c). Compound **13c** (1.7 g, 65%) was obtained as a colorless oil from **12c** (2.2 g, 3.0 mmol) as described above for the synthesis of **13b**, after purification by column chromatography (SiO_2, 0–1% AcOEt in hexane): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.23 (m, 20H), 5.53 (d, 1H, J=5.1 Hz), 4.07–3.51 (m, 7H), 1.39 (m, 21H), 0.99 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 143.9, 143.7, 133.4, 132.3, 130.7, 128.7, 128.7, 128.6, 128.4, 127.6, 127.5, 127.0, 126.8, 126.7, 87.1, 80.7, 77.6, 77.2, 71.2, 71.0, 38.8, 30.5, 29.0, 23.9, 23.1, 18.4, 18.3, 18.3, 18.2, 18.1, 18.1, 18.0, 17.9, 14.2, 12.5, 12.4, 12.4, 12.3, 12.2, 11.1; LRMS (FAB, positive) m/z 897 (MNa^+). Anal. Calcd for $C_{49}H_{70}O_5SeSi_2$: C, 67.32; H, 8.07. Found: C, 67.68; H, 8.37.

3.1.5. Phenyl 2-*O*-allyldimethylsilyl-3,4-bis-*O*-*tert*-butyldimethylsilyl-6-*O*-triphenylmethyl-1-seleno-β-D-glucopyranoside (10a). A mixture of **13a**[6f] (1.2 g, 1.5 mmol), allyldimethylchlorosilane (438 μL, 3.0 mmol) and MS 3A (20 mg) in pyridine (10 mL) was stirred at room temperature for 1 h. 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, 2–5% AcOEt in hexane) to give **10a** (1.3 g, 97%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78–7.17 (m, 20H, aromatic), 5.84–5.69 (m, 1H, allyl-CH), 5.29 (d, 1H, 1-CH, J=5.7 Hz), 5.25–4.79 (m, 2H, allyl-CH_2), 3.97 (dd, 1H, 2-CH, J=2.9, 5.7 Hz), 3.95 (ddd, 1H, 5-CH, J=1.2, 5.2, 6.7 Hz), 3.80 (dd, 1H, 3-CH, J=2.0, 2.9 Hz), 3.76 (dd, 1H, 4-CH, J=1.2, 2.0 Hz), 3.48 (dd, 1H, 6-CH, J=6.7, 9.6 Hz), 3.24 (dd, 1H, 6-CH, J=5.2, 9.6 Hz), 1.67–1.60 (m, 2H, allyl-CH_2), 0.82 (s, 9H, –*t*Bu), 0.81 (s, 9H, –*t*Bu), 0.18 (s, 3H, –$SiCH_3$), 0.17 (s, 3H, –$SiCH_3$), 0.13 (s, 3H, –$SiCH_3$), 0.00 (s, 6H, –$SiCH_3$ x 2), −0.06 (s, 3H, –$SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 133.9, 133.1, 132.5, 131.4, 128.8, 128.7, 128.7, 127.6, 127.5, 126.7, 126.6, 113.6, 86.7, 83.5, 81.5, 75.9, 71.0, 65.3, 60.4, 26.0, 26.0, 25.3, 21.2, 18.1, 18.0, 14.8, −1.4, −4.2, −4.3, −4.6; LRMS (FAB, positive) m/z 911 (MNa^+). Anal. Calcd for $C_{48}H_{68}O_5SeSi_3$: C, 64.90; H, 7.72. Found: C, 64.85; H, 7.88.

3.1.6. Phenyl 2-*O*-allyldimethylsilyl-3,4-bis-*O*-*tert*-butyldiphenylsilyl-6-*O*-triphenylmethyl-1-seleno-β-D-glucopyranoside (10b). Compound **10b** (1.2 g, 57%) was obtained as a white foam from **13b** (1.9 g, 1.8 mmol) as described above for the synthesis of **10a**, after purification by column chromatography (SiO_2, 2–5% AcOEt in hexane): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05–8.02 (m, 2H, aromatic), 7.93–7.24 (m, 38H, aromatic), 5.91–5.80 (m, 1H, allyl-CH), 5.55 (d, 1H, 1-CH, J=7.6 Hz), 5.00–4.95 (m, 2H, allyl-CH_2), 4.36 (d, 1H, 2-CH, J=7.6 Hz), 4.23–4.17 (m, 2H, 3-CH, 5-CH), 3.72 (d, 1H, 4-CH, J=3.2 Hz), 3.71 (t, 1H, 6-CH_2, J=9.5 Hz), 2.68 (dd, 1H, 6-CH_2, J=2.5, 9.5 Hz), 1.50–1.46 (m, 2H, allyl-CH_2), 1.11 (s, 9H, –*t*Bu), 0.93 (s, 9H, –*t*Bu), 0.10 (s, 3H, –$SiCH_3$), 0.09 (s, 3H, –$SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1, 135.8, 135.7, 135.5, 134.2, 132.9, 132.9, 132.8, 132.8, 131.0, 129.4, 129.4, 128.8, 128.7, 127.5, 127.4, 127.4, 127.3, 127.3, 126.8, 126.5, 113.2, 86.3, 84.1, 84.0, 76.2, 75.8, 71.1, 66.9, 26.9, 25.4, 19.2, 19.1, −1.6, −1.7; LRMS (FAB, positive) m/z 1159 (MNa^+). Anal. Calcd for $C_{68}H_{76}O_5SeSi_3$: C, 71.86; H, 6.74. Found: C, 71.62; H, 6.72.

3.1.7. Phenyl 2-*O*-allyldimethylsilyl-3,4-bis-*O*-triisopropylsilyl-6-*O*-triphenylmethyl-1-seleno-β-D-glucopyranoside (10c). Compound **10c** (1.4 g, 73%) was obtained as a colorless oil from **13c** (1.7 g, 1.9 mmol) as described above for the synthesis of **10a**, after purification by column chromatography (SiO_2, 2–5% AcOEt in hexane): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76–7.18 (m, 20H, aromatic), 5.81–5.70 (m, 1H, allyl-CH), 5.23 (d, 1H, 1-CH, J=7.6 Hz), 4.86–4.79 (m, 2H, allyl-CH_2), 4.12 (dd, 1H, 2-CH, J=4.5, 7.6 Hz), 3.98–3.94 (m, 2H, 3-CH, 5-CH), 3.86 (brs, 1H, 4-CH), 3.56 (dd, 1H, 6-CH, J=7.9, 9.4 Hz), 3.05 (dd, 1H, 6-CH, J=4.7, 9.4 Hz), 1.65 (m, 2H, allyl-CH_2), 1.03–0.84 (m, 42H, –$CH(CH_3)_2$), 0.15 (s, 3H, –$SiCH_3$), 0.11 (s, 3H, –$SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 134.3, 132.9, 130.6, 128.7, 128.7, 127.5, 127.4, 126.8, 126.6, 126.5, 113.3, 86.6, 83.7, 83.3, 77.1, 71.4, 66.4, 25.9, 18.5, 18.5, 18.3, 18.3, 12.8, 12.7, 12.3, −1.1, −1.3; HRMS calcd $C_{54}H_{80}NaO_5SeSi_3$: 995.4376 (MNa^+), found 995.4352.

3.1.8. Phenyl 2-*O*-allyldimethyl-3,4,6-tri-*O*-benzyl-1-seleno-β-D-glucopyranoside (15). A mixture of **14** (800 mg, 1.37 mmol), Et_3N (190 μL, 2.06 mmol), DMAP (17 mg, 0.137 mmol) and allyldimethylchlorosilane (300 μL, 2.06 mmol) was stirred at room temperature for 3 h. 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, 2–5% AcOEt in hexane) to give **15** (923 mg, 98%) as a colorless oil: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.66–7.07 (m, 20H, aromatic), 5.75 (m, 1H, allyl-H), 4.95 (d, 1H, benzyl-CH_2, J=11.5 Hz), 4.83 (d, 2H, allyl-CH_2, J=12.3 Hz) 4.83 (d, 2H, benzyl-CH_2, J=12.5 Hz), 4.78 (d, 1H, 1-CH, J=10.9 Hz), 4.59 (d, 1H, benzyl-CH_2, J=11.9 Hz), 4.55 (d, 1H, benzyl-CH_2, J=11.5 Hz), 4.51 (d, 1H, benzyl-CH_2, J=11.9 Hz), 3.74 (dd, 1H, 5-CH, J=9.7, 3.6 Hz), 3.74 (dd, 1H, 3-CH, J=10.9, 9.5 Hz), 3.73 (dd, 1H, 2-CH, J=10.9, 10.9 Hz), 3.73 (dd, 1H, 4-CH, J=9.5, 9.7 Hz), 3.49 (dd, 2H, 6-CH_2, J=3.6, 8.9 Hz), 1.67 (dd, 2H, Si–CH_2–, J=1.3, 7.6 Hz), 0.15 (s, 3H, Si–CH_3), 0.11 (s, 3H, Si–CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 138.2, 137.9, 134.2, 133.7, 129.3, 128.9, 128.4, 128.3, 128.2, 127.9, 127.7, 127.6, 127.5, 127.2, 126.8, 113.7, 87.0, 85.47, 80.3, 78.3, 75.2, 74.9, 74.8, 73.5, 68.9, 25.4, −1.3, −1.4; LRMS (FAB, positive) m/z 711 (MNa^+).

3.2. General procedure for the radical reactions of 10a–c

To a refluxing solution of **10a–c** (0.30 mmol) in benzene (6 mL), a solution of Bu_3SnH (161 μl, 0.6 mmol) and AIBN (33 mg, 0.2 mmol) in benzene (1.5 mL) was added dropwise by a syringe pump over 2 h. 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, 2–5% AcOEt in hexane) to give **16a–c** as colorless oil. **16a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.15 (m, 15H), 3.98 (ddd, 1H, J=3.2, 3.7, 9.9 Hz), 3.85 (d, 1H, J=3.7 Hz), 3.63 (d, 1H, J=3.7 Hz), 3.52 (dd, 1H, J=3.2, 9.9 Hz), 3.39 (d, 1H, J=9.9 Hz), 3.35 (d, 1H, J=3.7 Hz), 3.02 (d, 6H, J=3.7 Hz), 2.03 (m, 2H), 0.76 (s, 9H), 0.74 (s, 9H), 0.15 (s, 3H), 0.05 (s, 3H), −0.02 (s, 3H), −0.05 (s, 6H), −0.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1, 128.6, 127.5, 126.6, 86.1, 77.5, 77.3, 74.4, 72.2, 71.2, 70.4, 63.3, 33.6, 26.1, 26.0, 25.9, 18.5, 18.1, 18.1, 18.0, 0.0, −1.0, −3.7, −3.9, −4.2, −4.3; LRMS (FAB, positive) m/z 755 (MNa^+). Anal. Calcd for $C_{42}H_{64}O_5Si_3$: C, 68.80; H, 8.80. Found: C, 68.52; H, 8.98. **16b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.08 (m, 35H), 4.08 (ddd, 1H, J=1.3, 2.9, 9.5 Hz), 3.97 (t, 1H, J=4.6 Hz), 3.89 (d, 1H, J=1.3 Hz), 3.69 (t, 1H, J=9.5 Hz), 3.41 (t, 1H, J=1.3 Hz), 3.39 (t, 1H, J=1.3 Hz), 2.43 (dd, 1H, J=2.9, 9.5 Hz), 2.16–2.08 (m, 1H), 2.02–1.96 (m, 1H), 1.76–1.69 (m, 1H), 1.38–1.26 (m, 1H), 0.91 (s, 9H), 0.84–0.78 (m, 1H), 0.73 (s, 9H), 0.58–0.52 (m, 1H), 0.07 (s, 3H), −0.22 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 144.1, 135.7, 135.5, 135.4, 133.7, 133.6, 133.1, 133.0, 129.5, 129.4, 129.2, 129.1, 128.6, 127.4, 127.3, 127.3, 127.1, 126.5, 85.9, 79.1, 72.2, 70.3, 70.1, 66.8, 62.1, 34.7, 27.0, 26.8, 19.3, 19.2, 17.7, 16.9, −0.1, −1.0; LRMS (FAB, positive) m/z 1003 (MNa^+). Anal. Calcd for $C_{62}H_{72}O_5Si_3$: C, 75.87; H, 7.39. Found: C, 75.58; H, 7.58. **16c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.43 (m, 2H), 7.27–7.18 (m, 9H), 4.24 (m, 1H), 3.86 (brs, 2H), 3.68 (t, 1H, J=9.9 Hz), 3.53 (brs, 2H), 2.86 (dd, 1H, J=3.2, 9.9 Hz), 2.06–2.03 (m, 1H), 1.98–1.95 (m, 1H), 1.73–1.69 (m, 1H), 1.03–0.87 (m, 44H), 0.11 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 128.8, 128.6, 127.5, 127.4, 126.5, 86.1, 79.7, 72.7, 71.4, 70.2, 66.9, 62.2, 34.7, 18.3, 18.2, 18.1, 17.8, 16.9, 12.6, 12.6, 12.5, 12.4, 12.4, −0.1, −0.4; LRMS (FAB, positive) m/z 839 (MNa^+). Anal. Calcd for $C_{48}H_{76}O_5Si_3$: C, 70.53; H, 9.37. Found: C, 70.61; H, 9.45.

3.2.1. 4,8-Anhydro-6,7,9-tri-*O*-benzyl-2,3-dideoxy-D-*glycero*-D-*ido*-nonitol (18) and 4,8-anhydro-6,7,9-tri-*O*-benzyl-2,3-dideoxy-D-*glycero*-D-gulo-nonitol (19). To a refluxing solution of **15** (206 mg, 0.3 mmol) in a solvent (60 mL), a solution of Bu_3SnH (97 μL, 0.36 mmol) and AIBN (30 mg, 0.18 mmol) in the same solvent (8.4 mL) was added dropwise by a syringe pump over 4 h. The mixture was evaporated, and a mixture of the resulting residue, KF (349 mg, 6.0 mmol), $KHCO_3$ (180 mg, 1.8 mmol) and aqueous H_2O_2 (30%, 2.2 mL) in MeOH (1.7 mL) and THF (1.7 mL) was stirred at room temperature for 12 h. Aqueous saturated $Na_2S_2O_3$ was added, and the resulting mixture was filtrated through Celite. The filtrate 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, 20–35% AcOEt in $CHCl_3$) to give a mixture of **18** and **19** (yield, see Table 1) as a white solid. The α/β ratio was determined by HPLC analysis [YMC Pack R-ODS-5A; 85% aqueous MeOH, 1.0 mL/min, room temperature, 260 nm; retention time, 11 min (**18**), 13.5 min (**19**)]. From a mixture of **18** and **19** (78 mg, **18**:**19**=1:2.9), **18** (12 mg, white solid) and **19** (35 mg, white solid) were obtained in a pure form by preparative HPLC (YMC Pack D-ODS-5A, 20×250 mm; 95% aqueous MeOH, 10 mL/min, room temperature, 260 nm). **18**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.21 (m, 15H, aromatic), 4.68–4.52 (m, 6H, benzyl-CH_2), 4.03 (q, 1H, 8-CH_2, J=5.0 Hz), 3.91 (ddd, 1H, 4-CH, J=3.3, 3.6, 5.0 Hz), 3.78–3.58 (m, 7H, 1-, 9-CH_2, 5-, 6-, 7-CH), 1.68 (m, 4H, 2-, 3-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 137.5, 137.0, 128.2, 128.2, 128.0, 127.6, 127.6, 127.6, 127.5, 127.4, 127.3, 77.7, 74.9, 73.3, 73.1, 73.1, 72.8, 71.7, 69.8, 67.9, 62.5, 29.2, 24.8; LRMS (FAB, positive) m/z 493 (MH^+). Anal. Calcd for $C_{30}H_{36}O_6\cdot 1/2H_2O$: C, 71.83; H, 7.43. Found: C, 71.84; H, 7.44. **19**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.17 (m, 15H, aromatic), 4.97–4.52 (m, 6H, benzyl-CH_2), 3.69 (dd, 1H, 9-CH_2, J=2.0, 10.8 Hz), 3.68–3.62 (m, 3H, 1-CH_2, 9-CH_2), 3.58 (dd, 1H, 7-CH, J=9.4, 9.4 Hz), 3.46 (dd, 1H, 6-CH, J=8.8, 9.4 Hz), 3.43 (ddd, 1H, 8-CH, J=2.0, 4.5, 9.4 Hz), 3.32 (dd, 1H, 5-CH, J=8.8, 9.1 Hz), 3.22 (ddd, 1H, 4-CH, J=2.1,2.1, 9.1 Hz), 1.98 (m, 1H, 3-CH_2), 1.72 (m, 2H, 2-CH_2), 1.55 (m, 1H, 3-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 137.6, 137.5, 128.3, 128.1, 128.0, 127.6, 127.6, 127.5, 127.3, 86.5, 79.2, 78.5, 78.1, 76.5, 75.0, 74.6, 73.4, 73.3, 68.7, 62.5, 28.7, 28.5; LRMS (FAB, positive) m/z 493 (MH^+). Anal. Calcd for $C_{30}H_{36}O_6\cdot 1/2H_2O$: C, 71.83; H, 7.43. Found: C, 71.84; H, 7.44.

3.2.2. (2*R*,3*S*,4*R*,5*R*,6*R*)-3-acetoxy-6-(triphenylmethoxy)-methyl-4,5-di-*tert*-butyldimethylsilyloxy-2-[(3-dimethylphenylsilyl)propyl)tetrahydropyran (20). A mixture of **16a** (655 mg, 0.73 mmol) and PhLi (0.72 M in Et_2O, 5 mL, 3.6 mmol) in THF (14 mL) was stirred at −20 °C for 5 min, and then aqueous saturated NH_4Cl was added. The resulting mixture was partitioned between AcOEt and H_2O, and the organic layer was washed with brine, dried (Na_2SO_4) and evaporated. A mixture of the residue and AcCl (142 μL, 2.0 mmol) in pyridine (10 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. The residue was purified by column chromatography (SiO_2, 0–1% AcOEt in hexane) to give **20** (524 mg, 86%) as yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.08 (m, 20H), 4.21 (s, 1H), 4.04 (dd, 1H, J=3.5, 8.7 Hz), 3.70 (s, 1H), 3.65 (s, 1H), 3.48 (dd, 1H, J=8.7, 10.1 Hz), 3.28 (s, 1H), 2.98 (dd, 1H, J=3.5, 10.1 Hz), 1.97 (s, 3H), 1.70–1.40 (m, 2H), 1.36–1.18 (m, 2H), 0.89–0.79 (m, 2H), 0.78 (s, 9H), 0.62 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H), −0.05 (s, 3H), −0.06 (s, 3H), −0.07 (s, 3H), −0.11 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 144.3, 128.8, 128.7, 127.6, 126.7, 86.2, 77.6, 74.4, 72.2, 71.2, 70.2, 63.3, 33.6, 29.1, 27.4, 26.7, 26.2, 25.9, 18.3, 18.0, 18.0, 17.9, 13.7, 9.4, −0.1, −1.1, −3.9, −4.0, −4.4, −4.4; HRMS (FAB) calcd $C_{50}H_{72}O_6Si_3Na$ 875.4534 (MNa^+), found 875.4549.

3.2.3. (2*R*,3*S*,4*R*,5*R*,6*R*)-3-acetoxy-6-(triphenylmethoxy)-methyl-4,5-di-*tert*-butyldimethylsilyl-2-[3-(dimetyl-*p*-methoxyphenylsilyl)propyl]tetrahydropyrane (21). Compound **21** (328 mg, 77%) was obtained as yellow oil from **16a** (366 mg) as described above for the synthesis of **20** using *p*-MeOPhLi (prepared from *p*-lithioanisole and BuLi) instead of PhLi, after purification by column chromatography (SiO_2, 0–1% AcOEt in hexane): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.41 (m, 6H), 7.32–7.14 (m, 11H), 6.87 (t, 1H, J=7.2 Hz), 6.77 (d, 1H, J=8.2 Hz), 4.28 (s, 1H), 4.07 (dd, 1H, J=4.3, 9.5 Hz), 3.76 (s, 1H), 3.72 (brs, 4H), 3.55 (t, 1H, J=9.5 Hz), 3.34 (s, 1H), 3.02 (dd, 1H, J=4.3, 9.5 Hz), 2.03 (s, 3H), 1.68–1.66 (m, 1H), 1.43–1.41 (m, 1H), 1.27–1.23 (m, 2H), 0.84 (s, 9H), 0.77–0.73 (m, 2H), 0.67 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H), 0.00 (s, 3H), −0.01 (s, 3H), −0.03 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 170.8, 164.1, 144.0, 135.0, 130.5, 128.5, 127.6, 126.8, 126.7, 120.3, 109.3, 86.3, 79.1, 77.2, 71.2, 69.8, 68.6, 65.4, 61.5, 55.0, 34.8, 26.0, 25.8, 21.2, 20.3, 18.3, 17.8, 15.8, −2.5, −2.6, −4.5, −4.6, −4.8, −4.9; LRMS (FAB, positive) m/z 905 (MNa^+). Anal. Calcd for $C_{51}H_{74}O_7Si_3$: C, 69.34; H, 8.44. Found: C, 69.52, H, 8.52.

3.2.4. 4,8-Anhydro-4-*O*-acetyl-6,7-di-*O*-*tert*-butyldimethylsilyl-9-*O*-triphenylmethyl-2,3-dideoxy-D-*glycero*-D-*ido*-nonitol (22). To a mixture of **21** (54 mg, 0.060 mmol), KBr (15 mg, 0.12 mmol) and AcONa (50 mg, 0.61 mmol) in AcOH (12 mL) was added dropwise a mixture of AcOOH (32% in AcOH, 165 μL, 0.61 mmol) and H_2SO_4 (1.5 μL, 0.03 mmol) in AcOH at 0 °C, and the resulting mixture was stirred at room temperature for 14 h. After addition of aqueous saturated $Na_2S_2O_3$, 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 **22** (23 mg, 61%) as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.18 (m, 15H), 4.32 (s, 1H), 4.10 (dd, 1H, J=4.4, 9.1 Hz), 3.77 (brs, 2H), 3.62 (t, 2H, J=5.7 Hz) 3.56, (t, 1H, J=9.1 Hz), 3.34 (s, 1H), 3.10 (dd, 1H, J=4.4, 9.1 Hz), 2.05 (s, 3H), 1.73–1.68 (m, 2H), 1.45–1.43 (m, 2H), 0.88 (s, 9H), 0.84 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H), −0.01 (s, 3H), −0.05 (s, 3H); LRMS (FAB, positive) m/z 753 (MNa^+).

3.2.5. 4,8-Anhydro-4-*O*-acetyl-9-*O*-triphenylmethyl-2,3-dideoxy-D-*glycero*-D-*ido*-nonitol (23). A solution of **22** (32 mg, 44 μmol), TBAF (1 M in THF, 100 μL, 100 μmol) and AcOH (29 μL, 50 μmol) in THF (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 brine, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (SiO_2, 0–1% AcOEt in hexane) to give **23** (22 mg, 99%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.43 (m, 6H), 7.33–7.23 (m, 9H), 4.88 (dd, 1H, J=5.9, 9.7 Hz), 4.15 (ddd, 1H, 2.6, 3.5, 5.9), 3.78 (m, 1H), 3.68 (d, 2H, J=2.7 Hz), 3.56–3.52 (m, 2H), 3.39 (dd, 2H, J=4.4, 11.4 Hz), 2.72 (brs, 1H), 2.44 (brs, 1H), 2.11 (s, 3H), 1.72 (m, 2H), 1.56 (m, 2H); HRMS (FAB) calcd $C_{30}H_{34}O_6Na$: 529.2202 (MNa^+), found 529.2224.

3.2.6. 4,8-Anhydro-2,3-dideoxy-D-*glycero*-D-*ido*-nonitol 1,6,7-trisphosphate derivative 24. A mixture of **23** (15 mg, 30 μmol), XEPA (29 mg, 120 μmol) and 1*H*-tetrazole (10 mg, 135 μmol) in CH_2Cl_2 was stirred at 0 °C for 30 min. After addition of H_2O (10 μL), the mixture was stirred at room temperature for further 10 min. The resulting mixture was cooled to −40 °C, and then *m*-CPBA (35 mg, 200 μmol) was added. The mixture was warmed to room temperature over 30 min and partitioned between AcOEt and aquerous saturated Na_2SO_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 thin layer chromatography (SiO_2, 75% AcOEt in hexane) to give **24** (22 mg, 99%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.35 (m, 6H), 7.28–7.13 (m, 20H), 7.07–7.05 (m, 1H), 5.39 (dd, 1H, J=8.9, 13.8 Hz), 5.23–4.80 (m, 11H), 4.69 (t, 1H, J=13.8 Hz), 4.54–4.38 (m, 2H), 4.24–4.15 (m, 3H), 3.78–3.75 (m, 1H), 3.42 (dd, 1H, J=1.2, 10.3 Hz), 3.34 (dd, 1H, J=7.3, 10.3 Hz), 2.12 (s, 3H), 1.94–1.77 (m, 2H), 1.70–1.65 (m, 2H); ^{31}P NMR (202 MHz, D_2O, H-decoupled) δ 0.32 (s), −2.19 (s), −3.82 (s); HRMS (FAB) calcd $C_{54}H_{55}O_{16}P_3Na$: 1075.2601 (MNa^+), found 1075.2530.

3.2.7. 4,8-Anhydro-2,3-dideoxy-D-*glycero*-D-*ido*-nonitol 1,6,7-trisphosphate hexasodium salt (9). A mixture of **24** (18 mg, 17 μmol) and Pd–C (10%, 20 mg) in MeOH (2 mL) was stirred at room temperature under atmospheric pressure of H_2 for 40 min. 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 (1 μL, 13 μmol) and then the mixture was evaporated. A solution of the residue in H_2O was washed with AcOEt (three times) and evaporated. A solution of the residue in aqueous NaOH (1 M, 2 mL) was stirred at room temperature for 12 h. The resulting mixture was applied to Diaion PK-212 (H^+-form) column, and the column was developed with H_2O. The fractions containing **9** (acidic fractions) were evaporated. A solution of the residue in H_2O (1 mL) was applied to Daiaion WK-100 (Na^+-form) column, and the column was developed with H_2O. The fractions containing **9** were evaporated and dried in vacuo to give **9** (sodium salt, 12 mg, quant.) as a white solid. ^{1}H NMR (400 MHz, D_2O) δ 4.17 (dd, 1H, J=8.5, 17.3 Hz), 3.90 (dd, 1H, J=5.4, 10.6 Hz), 3.83–3.63 (m, 5H), 3.59–3.49 (m, 2H), 1.70–1.44 (m, 4H); ^{13}C NMR (100 MHz, D_2O) δ 77.46 (dd, $J_{c,p}$=3.3, 4.9 Hz), 75.18 (s), 73.26 (d, $J_{c,p}$=2.5 Hz), 73.03 (d, $J_{c,p}$=2.5 Hz), 71.72 (s), 65.53 (d,

$J_{c,p}$=5.8 Hz), 26.78 (d, $J_{c,p}$=6.6 Hz), 21.63 (s); ^{31}P NMR (202 MHz, D_2O, H-decoupled) δ 2.54 (s), 2.45 (s), 2.13 (s); HRMS (FAB) calcd $C_9H_{17}O_{15}Na_3P_3$: 526.9473 (M^-), found 526.9444.

3.3. Materials for the bioassay

RPMI 1640 medium, L-glutamine, 2-mercaptoethanol and G-418 were from Invitrogen (Paisley, UK), sera were from Sigma (Poole, UK) and Mag-fluo-4AM was from Molecular Probes (Leiden, The Netherlands).

3.3.1. Stable transfection of DT40 cells with rat type 1 IP_3R. The open reading frame of rat type 1 IP_3R (IP_3R1) was amplified by polymerase chain reaction (PCR) from the expression vector pCMVI-9-IP_3R1[28] using the following primers: 5′-AGGAATTCGCCACCATGTCTGACAAA ATG-3′ and 5′-CCGGTACCGAATTCTTAGGCTGGCTG CTGT-3′ and cloned as an *Eco*RI fragment into pcDNA3 (Invitrogen). The chicken β-actin hybrid promoter[29] was excised from the vector pAneo[31] and cloned in place of the CMV promoter upstream of the $InsP_3R1$ open reading frame to create the construct pcDNA3-IP_3R1. DT40 cells in which the genes for all three endogenous IP_3R subtypes have been deleted (DT40/IP_3R-KO)[30] were stably transfected by electroporation with linearized pcDNA3-IP_3R1 using a Gene Pulser apparatus (Bio-Rad Laboratories) at 330 V, 500 μF with 5 μg DNA/10^6 cells. Clonal isolation was carried out in the presence of 2 mg/ml G-418 and positive clones were amplified and screened for the presence of rat $InsP_3R1$ by western blotting using an anti-peptide antiserum[31] corresponding to the C-terminal 15-residues of rat IP_3R1.

3.4. Cell culture

DT40/IP_3R-KO cells stably expressing recombinant rat IP_3R1 (DT40/IP_3R1 cells) were cultured in suspension in RPMI 1640 medium supplemented with foetal bovine serum (10%), L-glutamine (2 mM), 2-mercaptoethanol (50 μM) and heat-inactivated chicken serum (1%). Cells were incubated in a humidified atmosphere (95% O_2; 5% CO_2 at 37 °C) and passaged every 2–3 days when they had reached a density of $\sim 2\times10^6$ cells/ml.

3.5. Measurement of Ca^{2+} release from permeabilized cells

The effects of $InsP_3$ on intracellular Ca^{2+} stores were measured using a low-affinity Ca^{2+}-indicator trapped within the intracellular stores of permeabilized cells. DT40/IP_3R1 cells were harvested (650× *g*; 2 min) and re-suspended (2–3×10^7 cells/ml) in Hepes-buffered saline (HBS: 135 mM NaCl, 5.9 mM KCl, 1.2 mM $MgCl_2$, 1.5 mM $CaCl_2$, 11.6 mM Hepes, 11.5 mM D-glucose, pH 7.3) supplemented with Mag-fluo-4AM (20 μM), Pluronic F-127 (0.05%) and bovine serum albumin (1 mg/ml). After 1 h at 20 °C in the dark, the Mag-fluo-4-loaded cells were harvested (650×*g*; 2 min) and re-suspended ($\sim 2\times10^6$ cells/ml) in Ca^{2+}-free cytosolic-like medium (CLM: 140 mM KCl, 20 mM NaCl, 2 mM $MgCl_2$, 1 mM EGTA, 20 mM Pipes, pH 7.0). The cells were permeabilized by incubation with saponin (10 μg/ml, 4 min at 37 °C), harvested (650×*g*; 2 min) and resuspended in Mg^{2+}-free CLM (140 mM KCl, 20 mM NaCl, 1 mM EGTA, 375 μM $CaCl_2$ ($\sim$200 nM free [Ca^{2+}]), 20 mM Pipes, pH 7.0). The permeabilized cells (with Mag-fluo-4 trapped within the lumen of the endoplasmic reticulum, ER) were then attached to 96-well plates ($\sim 8\times10^5$ cells/well) coated with poly-L-lysine (0.01%) and centrifuged onto the plate (300×*g*; 2 min). Immediately before an experiment, the cells were washed twice in Mg^{2+}-free CLM to remove cytosolic Mag-fluo-4 and the plates were then mounted in a FlexStation fluorescence plate reader (Molecular Devices, Sunnyvale, CA), which allows automated additions to the sample wells while recording fluorescence. Mag-fluo-4 fluorescence was monitored by excitation at 485 nm with emission detected at 520 nm. Active Ca^{2+} uptake into the ER was initiated by addition of Mg^{2+}-ATP (1.5 mM) and after 150 s, when the stores had loaded to a steady-state Ca^{2+} content, IP_3 was added. The amount of Ca^{2+} released by IP_3 was expressed as a fraction of the total Ca^{2+} content of the ER as assessed by addition of 1 μM ionomycin. Data are presented as means ±s.e. means from at least three independent experiments, each performed in triplicate. Concentration–effect relationships were fitted to four-parameter logistic equations using non-linear curve-fitting procedures (GraphPad Prism, San Diego, CA).

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