Synthesis of Adenophostin Analogues Lacking the Adenine Moiety as Novel Potent IP_3 Receptor Ligands: Some Structural Requirements for the Significant Activity of Adenophostin A

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1-*O*-Tetrahydrofuranyl-α-D-glucopyranose derivatives **5**−**8** were designed and synthesized as novel IP_3 receptor ligands. The glycosidation reactions between fluoroglycosyl donor **23** and tetrahydrofuran derivatives **11**−**14** as glycosyl acceptors selectively gave the corresponding α-glycosides, which were converted into the target compounds **5**−**8** via the introduction of phosphate groups using the phosphoramidite method. Among these compounds, 1-*O*-tetrahydrofuranyl-α-D-glucopyranose trisphosphate derivatives **5** and **8** significantly inhibited the binding of [^{3}H] IP_3 to IP_3 receptor from porcine cerebella, with IC_{50} values of 25 and 27 nM, respectively, which were comparable to the affinity of IP_3 itself.

Introduction

Considerable attention has been focused on D-*myo*-inositol 1,4,5-trisphosphate (IP_3), an intracellular Ca^{2+}-mobilizing second messenger, because of its significant biological importance.[1,2] Therefore, analogues of IP_3 have been synthesized extensively to develop specific ligands for IP_3 receptors, which are very useful for proving the mechanism of IP_3-mediated Ca^{2+} signaling pathways.[3] However, none of these analogues has surpassed IP_3 itself either in binding affinity for IP_3 receptor or Ca^{2+}-mobilizing activity.[3,4] Furthermore, specific antagonists of the receptor have not yet been developed.[3,5]

Recently, Takahashi and co-workers isolated adenophostin A and B from *Penicillium brevicompactum* and found that they are very strong IP_3 receptor ligands; **2** and **3** are 10−100 times more potent than IP_3 with regard to both the affinity for IP_3 receptor and Ca^{2+}-mobilizing ability in cells.[6] From synthetic studies of IP_3 analogues, it is now clear that the vicinal 4,5-*trans*-diphosphate is essential for this activity and a third phosphate group at the 1-position enhances binding affinity.[3] Therefore, the α-D-glucopyranose structure of adenophostins may be a bioisostere of the D-*myo*-inositol moiety in IP_3, and the three-dimensional locations of the three phosphate groups of adenophostins may be the same as those of IP_3.[7]

Recently, two groups[8,9] designed and synthesized 2-(hydroxyethyl)-α-D-glucopyranoside 3,4,2′-trisphosphate (**4**) as a simplified analogue of adenophostins and showed that it was an agonist at IP_3 receptors with ∼10-fold lower potency than IP_3. We hypothesized that the lower affinity of **4** for the receptor compared to those of adenophostins may be due to the conformational flexibility of the side-chain moiety of **4**. This flexibility of the side chain may not allow the third phosphate to achieve efficient positioning for binding to the receptor. On the basis of these considerations, we designed 1-*O*-tetrahydrofuranyl-α-D-glucopyranose derivatives **5**, **7**, and **8** (Figure 1) as novel IP_3 receptor ligands in which the location of the third phosphate group in space is restricted because it is attached to the tetrahydrofuran ring, as in adenophostins. Compound **6**, which is a derivative of **5** that lacks a third phosphate group, was also designed to confirm the role of the phosphate group in binding to the receptor.

While this study was being carried out, the synthesis and biological activity of methyl 3-*O*-(α-D-glucopyranosyl)-*β*-D-ribofuranoside 2,3′4′-trisphosphate (**9**), which was also designed to restrict the conformation of the side-chain moiety of **4**, were reported.[4,10] Biological evaluations of these compounds **5**−**8**, together with previous results,[4,8−11] may help to clarify the structural requirements for the significant biological activity of adenophostins. In this paper, we describe the synthesis and preliminary biological effects of these compounds.[12]

Results and Discussion

We planned to synthesize these target compounds via glycosidation reactions with glycosyl donor **10** and tet-

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(1) Berridge, M. J. *Nature (London)* **1993**, *361*, 315−325.

(2) Sutko, J. L.; Airey, J. A. *Pharm. Rev.* **1996**, *76*, 1027−1071.

(3) Potter, B. V. L.; Lampe, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1933−1972 and references sited therein.

(4) Marchant, J. S.; Beecroft, M. D.; Riley, A. M.; Jenkins, D. J.; Marwood, R. D.; Taylor, C. W.; Potter, B. V. L. *Biochemistry* **1997**, *36*, 12780−12790.

(5) Although heparin and decavanadate have been demonstrated to inhibit IP_3 binding, they did not show specificity for the IP_3 receptor, and therefore their pharmacological uses are limited; see ref 3.

(6) (a) Takahashi, S.; Tanzawa, T.; Miyawaki, A.; Takahashi, M. *J. Antibiot.* **1993**, *46*, 1643−1647. (b) Takahashi, S.; Kinoshita, T.; Takahashi, M. *J. Antibiot.* **1993**, *46*, 95−100. (c) Takahashi, M.; Tanzawa, K.; Takahashi, S. *J. Biol. Chem.* **1994**, *269*, 369−372.

(7) A possibility that the 2′-phosphate group of adenophostin A may be positioned differently from the 1′-phosphate group of IP_3 has also been suggested by a molecular modeling study; see ref 8.

(8) Wilcox, R. A.; Erneux, C.; Primrose, W. U.; Gigg, R.; Nahorski, S. R. *Mol. Pharmacol.* **1995**, *47*, 1204−1211.

(9) (a) Jenkins, D. J.; Marwood, R. D.; Potter, B. V. L. *Carbohydr. Res.* **1996**, *287*, 169−182. (b) Murphy, C. T.; Riley, A. M.; Lindley, C. J.; Jenkins, D. J.; Westwick, J.; Potter B. V. L. *Mol. Pharmacol.* **1997**, *52*, 741−748.

(10) Jenkins, D. J.; Marwood, R. D.; Potter, B. V. L. *Chem. Commun.* **1997**, 449−450.

(11) Compound **9** showed potent IP_3 receptor binding and Ca^{2+}-mobilizing effects that were comparable to those of IP_3; see ref 4.

(12) A part of this study has been published as a communication: Tatani, K.; Shuto, S.; Ueno, Y.; Matsuda, A. *Tetrahedron Lett.* **1998**, *39*, 5065−5068.

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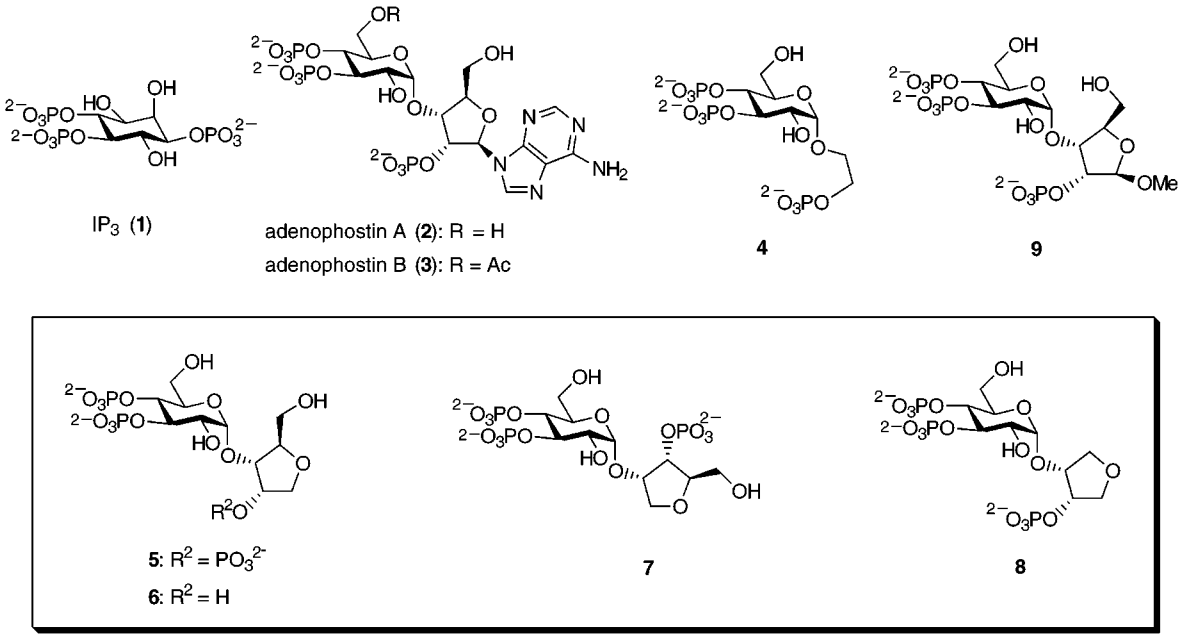


Figure 1.

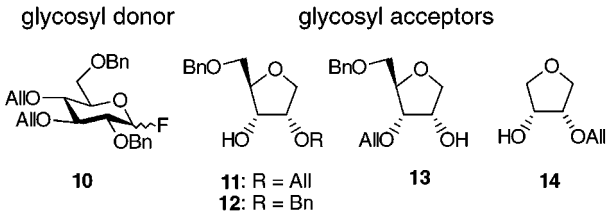
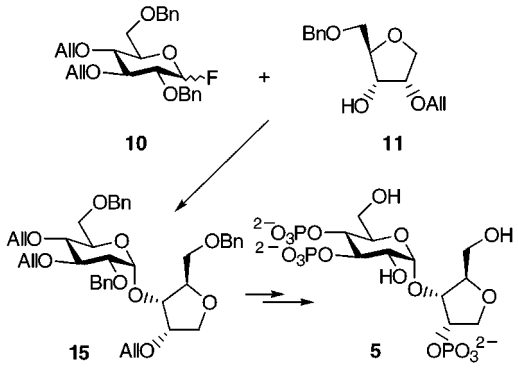


Figure 2.

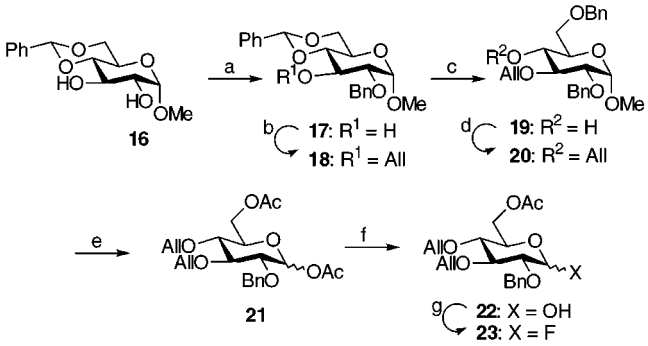
Scheme 1



rahydrofuran derivatives **11**−**14** as glycosyl acceptors (Figure 2). A typical synthetic route is shown in Scheme 1. We designed a fluoroglycoside **10** as a donor, since fluoroglycosides are stable and easy to prepare and have been know to be effective for the selective preparation of α-glycopyranosides.[13]

The preparation of the glycosyl donor is shown in Scheme 2. Ogawa and Kaburagi investigated regioselective benzylation of glucose derivative **16** by various methods.[14] As a result, they obtained 2-*O*-benzyl ether **17** in the highest yield (70%) by treating the 2,3-*O*-dibutylstannylidene derivative of **16** with BnBr in DMF.[14] We also found that the 2-hydroxyl group was benzylated with high selectivity when the same stannylidene derivative was heated with BnBr to give the desired 2′-*O*-benzyl product **17** in 95% yield from **16** along with a trace of the 3′-*O*-benzyl regioisomer when toluene was used as a benzylation reaction solvent. After the 3′-hydroxyl of **17** was protected with an allyl group, the benzylidene moiety of **18** was reductively cleaved with $NaBH_3CN/HCl$[15] in THF to give 6-*O*-benzyl derivative **19** in 61% yield along with the corresponding 4-*O*-benzyl isomer (5%). The 4-hydroxyl of **19** was allylated, and then the resulting fully protected sugar **20** was acetolysized with Ac_2O and H_2SO_4. Both the 6-*O*-Bn and 1-*O*-Me groups were replaced by an acetoxy group to give **21** in 79% yield. After the anomeric acetyl group of **21** was selectively removed with piperidine in THF, the product **22** was treated with DAST in CH_2Cl_2 to give fluoroglycoside **23** (the α/β ratio was 27:73 on the basis of its ^1H NMR spectrum) in 89% yield. Although fluoro sugar **10**, the 6-hydroxyl of which was protected by a benzyl group, was

Scheme 2[a]



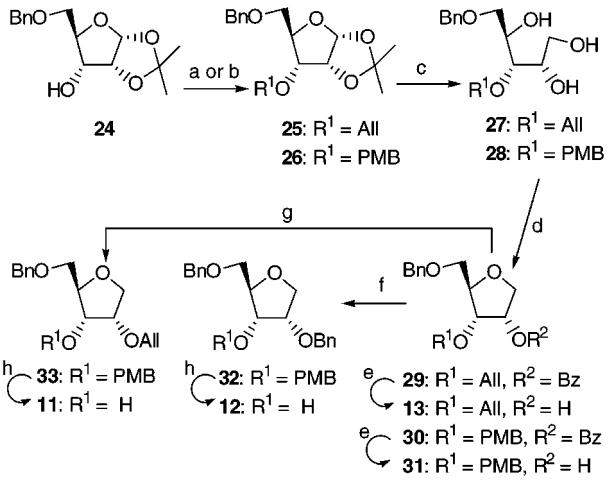
[a] Reagents: (a) (1) Bu_2SnO, benzene−MeOH, (2) BnBr, toluene; (b) NaH, AllBr, DMF; (c) $NaBH_3CN$, HCl, Et_2O; (d) NaH, AllBr, benzene; (e) Ac_2O, H_2SO_4; (f) piperidine, THF; (g) DAST, CH_2Cl_2.

(13) (a) Mukaiyama, T.; Murai, Y.; Shoda, S. *Chem. Lett.* **1981**, 431−432. (b) Hashimoto, S.; Hayashi, M.; Noyori, R. *Tetrahedron Lett.* **1984**, *25*, 1379−1382. (c) Kunz, H.; Sager, W. *Helv. Chim. Acta* **1985**, *68*, 283−287.

(14) Ogawa, T.; Kaburagi, T. *Carbohydr. Res.* **1982**, *103*, 53−64.

(15) Garegg, P. J.; Hultberg, H. *Carbohydr. Res.* **1981**, *93*, C10−C11.

Scheme 3[a]



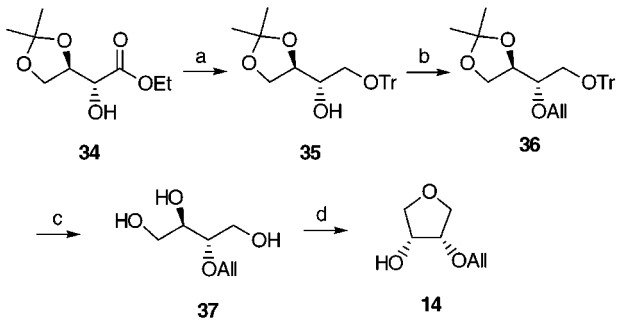
[a] Reagents: (a) NaH, AllBr, THF−DMF; (b) NaH, PMBCl, THF−DMF; (c) (1) HCl, aq THF, (2) $NaBH_4$, MeOH; (d) (1) Ph_3P, DEAD, THF, (2) BzCl, py; (e) NaOMe, MeOH; (f) NaH, BnBr, DMF; (g) NaH, AllBr, DMF; (h) DDQ, $CH_2Cl_2-H_2O$.

initially designed as the glycosyl donor at first (Figure 2), we used **23** as a glycosyl donor, since we presumed that an acetyl group was also suitable for protecting the 6-hydroxy of the fluoroglycosyl donor.

The glycosyl acceptors **11**−**13** were prepared from a known D-ribose derivative **24**[16] as shown in Scheme 3. The 3-hydroxyl of **24** was protected with an allyl or 4-methoxybenzyl (PMB) group to give the corresponding 3-*O*-allyl derivative **25** or 3-*O*-PMB derivative **26**, respectively. Although hydride reduction at the anomeric position of **25** or **26** in the presence of a Lewis acid was tried under various conditions, it was unsuccessful. However, the 1-position was successfully deoxygenated via the reductive ring-opening products **27** and **28**. Thus, successive treatment of **25** with HCl under reflux conditions in aqueous THF, followed by $NaBH_4$ in MeOH, gave the ring-opening product **27** in 74% yield. Treatment of **27** under Mitsunobu reaction conditions[17] gave the desired 1-deoxy derivative **13**, which was isolated as the corresponding 2-*O*-benzoyl derivative **29** in 71% yield from **27**. The benzoyl group was removed with NaOMe in MeOH to give the glycosyl acceptor **13**. Similarly, 3-*O*-PMB-1-deoxy derivative **31** was prepared from **28**. After the 2-hydroxy of **31** was protected with an allyl group, the 3-*O*-PMB group was oxidatively removed with DDQ in $CH_2Cl_2-H_2O$[18] to give glycosyl acceptor **11**. In a similar manner, glycosyl acceptor **12** was readily prepared from **31** via **32**.

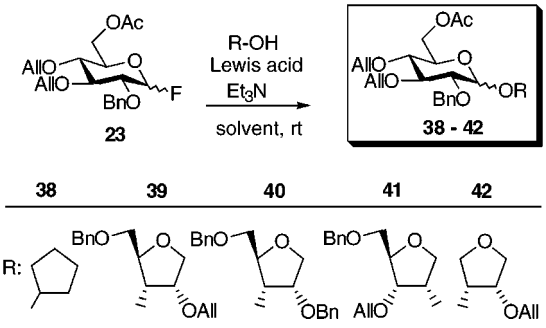
The glycosyl acceptor **14** was synthesized from an optically active triol derivative **34**, which was prepared from D-isoascorbic acid by a previously reported method,[19] as shown in Scheme 4. Successive treatment of **34** with $LiAlH_4$ in Et_2O, followed by TrCl in pyridine, gave tetrol derivative **35**. After the free secondary hydroxyl of **35** was protected with an allyl group, the isopropylidene and trityl groups were simultaneously removed with TsOH in MeOH to give **37**. Intramolecular condensation of **37** was investigated by various methods. Treatment of **37** under Mitsunobu reaction conditions, which are efficient for preparing tetrahydrofuran derivatives **29** and **30** as described above, did not give the desired **14**. However, when **37** was treated with Tf_2O in MeCN, tetrahydrofuran derivative **14** was obtained in 41% yield.

Scheme 4[a]



[a] Reagents: (a) (1) $LiAlH_4$, EtO, (2) TrCl, py; (b) NaH, AllBr, DMF; (c) TsOH, MeOH; (d) Tf_2O, Et_3N, DMAP, MeCN.

Scheme 5



Glycosidation reactions with fluoroglycosyl donor **23** were first examined with cyclopentanol as a model acceptor, and the results are summarized in Table 1. Reactions were performed with $BF_3{\cdot}Et_2O$[13c] or TMSOTf[13b] as a promoter, which is known to be effective for glycosidation with fluoroglycosyl donors, in the presence of Et_3N in CH_2Cl_2 (entries 1 and 2). As a result, TMSOTf proved to be more effective than $BF_3{\cdot}Et_2O$ in this reaction system to give the corresponding anomeric mixture of glycosides in high yield ($\alpha:\beta$ = 67:33). The reaction with TMSOTf as a promoter was investigated with several reaction solvents, and the α/β ratio was best when Et_2O was used as a solvent (entry 5). The reaction with glycosyl acceptor **11** under the same conditions as those in entry 5 gave the desired α-glycoside **39** selectively (entry 6; yield 88%, $\alpha:\beta$ = 95:5) (Scheme 5). Similar glycosidation reactions with glycosyl donor **23** and glycosyl acceptors **12**−**14** gave the corresponding glycosides **40**−**42** in high yields (entries 7−9), and the desired α-glycosides were mainly produced (α/β = 93:7, 85:15, and 94:6, respectively). However, these anomeric mixtures were inseparable at this stage.

The 6′-*O*-acetyl group of **39** was replaced with a benzyl group by the usual method, and removal of the allyl groups of the resulting product **15** was examined. The three allyl groups were found to be deprotected simultaneously when **15** was heated with Pd−C and TsOH

(16) Tino, J. A.; Clark, J. M.; Field, A. K.; Jacobs, G. A.; Lis, K. A.; Michalik, T. L.; McGeever-Robin, B.; Slusarchyk, W. A.; Spergel, S. H.; Sundeen, J. E.; Tuomari, A. V.; Weaver, E. R.; Young, M. G.; Zahler, R. *J. Med. Chem.* **1993**, *36*, 1221−1219.

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(18) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 889−892.

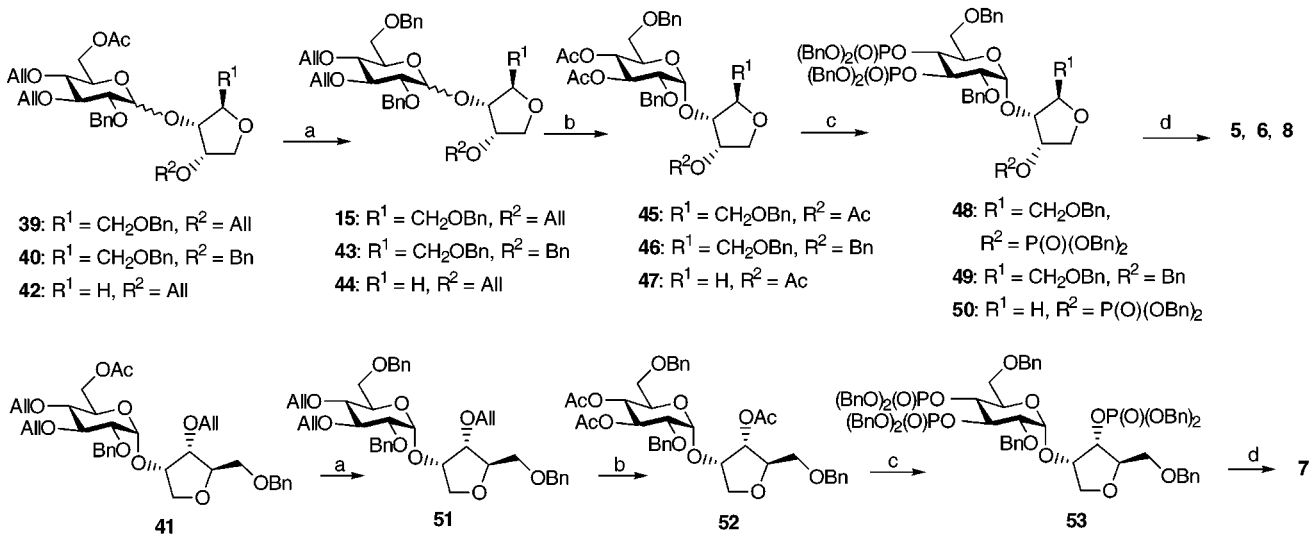
(19) Abushanab, E.; Vemishetti, P.; Leiby, R. W.; Singh, H. K.; Mikkilineni, A. B.; Wu, D. C.-J.; Saibaba, R.; Panzica, R. P. *J. Org. Chem.* **1988**, 53, 2598−2602.

Table 1. Synthesis of 38−42 by Glycosidation Reactions with Fluoro Sugar 23 as a Glycosyl Donor

entry	ROH	Lewis acid	solvent	time (h)	product	yield (%)	α/β[a]
1	cyclopentanol	$BF_3{\cdot}Et_2O$	CH_2Cl_2	11	**38**	74	68:32
2	cyclopentanol	TMSOTf	CH_2Cl_2	0.5	**38**	93	67:33
3	cyclopentanol	TMSOTf	toluene	1	**38**	62	60:40
4	cyclopentanol	TMSOTf	EtCN	0.5	**38**	63	54:46
5	cyclopentanol	TMSOTf	Et_2O	7	**38**	93	77:23
6	**11**	TMSOTf	Et_2O	1	**39**	88	95:5
7	**12**	TMSOTf	Et_2O	1.5	**40**	85	93:7
8	**13**	TMSOTf	Et_2O	0.7	**41**	89	85:15
9	**14**	TMSOTf	Et_2O	1.5	**42**	78	94:6

[a] Determined by the ^{1}H NMR spectrum.

Scheme 6[a]



[a] Reagents: (a) (1) NaOMe, MeOH, (2) NaH, BnBr, DMF; (b) (1) Pd−C, TsOH, aq EtOH, (2) Ac_2O, py; (c) (1) NaOMe, MeOH, (2) $(BnO)_2PN^iPr_2$, tetrazole, CH_2Cl_2, then m-CPBA; (d) H_2, Pd−C, EtOH.

under reflux conditions in aqueous EtOH,[20] and the product was isolated as triacetate **45** in 98% yield. At this stage, the desired α-anomer **45** was obtained in a pure form, after silica gel column chromatography. Phosphate units were introduced using the phosphoramidite method. Thus, after the three acetyl groups of **45** were removed, the resulting trihydroxy product was treated with dibenzyldiisopropylphosphoramidite and tetrazole in CH_2Cl_2 followed by oxidation with *m*-CPBA[21] to give the desired triphosphate derivative **48** in 74% yield from **45**. Finally, all of the benzyl groups of **48** were simultaneously removed by catalytic hydrogenation with Pd−C in EtOH to give the target compound **5** quantitatively as a sodium salt after treatment with ion-exchange resin.

Similarly, the glycosidation products **40**−**42** were converted into the target diphosphate derivatives **6** and triphosphate derivatives **8** and **7**, respectively (Scheme 6).

The binding affinity of the synthesized compounds for the IP_3 receptor of porcine cerebella was evaluated in vitro with [^{3}H] IP_3 as a radioligand,[22] and the results are summarized in Table 2. Compound **5**, which corresponds to the *des*-adenyl analogue of adenophostin A, significantly inhibited the binding of [^{3}H]IP_3 with an IC_{50} value of 25 nM, which is comparable to the affinity of IP_3 itself (IC_{50} = 19 nM). Compound **6**, which lacks the third phosphate group in **5**, was almost inactive (IC_{50} = 7.8 μM).[23] Compound **7**, a regioisomer of **5**, showed about 20-fold lower potency (IC_{50} = 0.54 μM) than **5**, which suggested that the binding affinity of the compounds depends on the three-dimensional location of the third phosphate group. Interestingly, compound **8**, which lacks the hydroxymethyl moiety of **5**, had a significant binding affinity (IC_{50} = 27 nM) similar to that of **5**. Thus, this study indicates that the α-D-glucopyranose structure is a good bioisostere of the *myo*-inositol backbone of IP_3 and also that adequate conformational restriction of the phosphate group of the side-chain moiety attached at the

Table 2. Binding Affinity of the Compounds for IP_3 Receptor from Porcine Cerebella[a]

compd	IC_{50} (μM)
5	0.025
6	7.8
7	0.54
8	0.027
IP_3	0.019
adenophostin A	0.0019

[a] Measured with [^{3}H]IP_3 (2.3 nM) as a radioligand in Tris−HCl buffer (50 mM, pH 8.0) containing EDTA (1.0 mM).

(20) Boss, R.; Scheffold, R. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 558−559.
(21) Yu, K.-L.; Fraser-Reed, B. A. *Tetrahedron Lett.* **1988**, *29*, 979−982.
(22) Worley, P. F.; Basadan, J. M.; Supattapone, S.; Wilson, V. S.; Snyder, S. H. *J. Biol. Chem.* **1987**, 262, 12132−12136.
(23) Under the voltage-clamp condition (holding potential: −70 mV), dialysis of 0.1 mM **6** induced inward currents in nine out of 12 isolated turtle olfactory neurons. The mean magnitude of the response to **6** (53.7 ± 35.8 pA) was nearly 60% of that to IP_3. This result suggested that **6** is an agonist of IP_3 receptor: Kashiwayanagi, M. Unpublished results.

1α-position improves the binding affinity for IP_3 receptor. Some apparent structure requirements for the binding affinity of adenophostins to the IP_3 receptor suggested by this study and previous results[4,8,−11] are that (1) the adenine moiety is not essential, but enhances affinity, (2) the three-dimensional location of the third phosphate group plays an important role in strong binding to the receptor, and (3) the hydroxymethyl group of the ribose moiety does not play a role in binding to the receptor.

Further biological evaluations of the compounds are now underway.

Experimental Section

Melting points are uncorrected. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded at 270, 400, and 500 MHz (^{1}H) and at 125 MHz (^{31}P). Chemical shifts are reported in ppm downfield from TMS (^{1}H and ^{13}C) or H_3PO_4 (^{31}P). Mass spectra were obtained by electron ionization (EI) or fast atom bombardment (FAB) methods. Thin-layer chromatography was done on Merck coated plate $60F_{254}$. Silica gel chromatography was done with Merck silica gel 5715. Reactions were carried out under an argon atmosphere.

Methyl 2-*O*-Benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (17). A mixture of **16** (10.0 g, 35.5 mmol) and Bu_2SnO (8.84 g, 35.5 mmol) in benzene−MeOH (10:1, 120 mL) was heated under reflux under azeotropic conditions for 3 h, and then the resulting mixture was evaporated under reduced pressure. A mixture of the residue and BnBr (42.2 mL, 355 mmol) was heated in toluene (75 mL) under reflux for 12 h, and the resulting solution was evaporated under reduced pressure. To a solution of the residue in EtOAc (360 mL) was added an aqueous KF solution (6.2 g of KF in 6.5 mL of H_2O), and the mixture was stirred at room temperature for 3.5 h. After filtration of the resulting insoluble materials, the filtrate was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/EtOAc 3:1) to give **17** (12.5 g, 95% as a white solid): $[\alpha]^{26}_D$ +35.2° (*c* 1.00, $CHCl_3$) [lit.[14] $[\alpha]^{25}_D$ +34.7° (*c* 0.95, $CHCl_3$)].

Methyl 3-*O*-Allyl-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (18). A solution of **17** (15.5 g, 41.7 mmol) in DMF (160 mL) was added dropwise to a suspension of NaH (60% in mineral oil, 5.00 g, 125 mmol) in DMF (50 mL) at 0 °C, and the mixture was stirred at the same temperature for 1.5 h. Allyl bromide (4.33 mL, 50.0 mmol) was added, and the resulting mixture was stirred at room temperature for 13 h. The reaction mixture was poured into saturated aqueous NH_4Cl (500 mL), and the resulting mixture was extracted with EtOAc (350 mL × 2). The organic layer was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was treated with EtOAc−hexane to give a crystalline **18** (15.2 g, 89% as a needle): $[\alpha]^{28}_D$ +1.1° (*c* 0.91, $CHCl_3$) [lit.[24] $[\alpha]^{23}_D$ +1.3° (*c* 0.96, $CHCl_3$)]; mp 98−99 °C [lit.[24] mp 96−98 °C].

Methyl 3-*O*-Allyl-2,6-di-*O*-benzyl-α-D-glucopyranoside (19). To a mixture of **18** (1.24 g, 3.01 mmol), $NaBH_3CN$ (1.89 g, 30.1 mmol), and molecular sieves 3 A powder (7.0 g) in THF (50 mL) was added a saturated HCl solution in Et_2O at 0 °C to adjust the pH of the mixture at ca. 3. The mixture was stirred at 0 °C for 1 h and filtered through Celite. The filtrate was washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/EtOAc 3:1) to give **19** (757 mg, 61% as an oil): $[\alpha]^{28}_D$ +28.1° (*c* 1.05, $CHCl_3$) [lit.[24] $[\alpha]^{23}_D$ +28.7° (*c* 1.81, $CHCl_3$)] and the corresponding 4-*O*-benzyl regioisomer (63 mg, 5% as a solid) [$[\alpha]^{32}_D$ +44.8° (*c* 1.03, $CHCl_3$) [lit.[24] $[\alpha]^{23}_D$ +48.4° (*c* 1.09, $CHCl_3$)].

Methyl 3,4-Di-*O*-allyl-2,6-di-*O*-benzyl-α-D-glucopyranoside (20). A mixture of **19** (481 mg, 1.16 mmol), NaH (60% in mineral oil, 278 mg, 6.95 mmol), and allyl bromide (0.120 mL, 1.39 mmol) in benzene (5.8 mL) was heated under reflux for 22 h. The reaction mixture was poured into saturated aqueous NH_4Cl (30 mL), and the resulting mixture was extracted with Et_2O (50 mL). The organic layer was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/EtOAc 4:1) to give **20** (427 mg, 81% as an oil): $[\alpha]^{26}_D$ +46.2° (*c* 1.05, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.22 (m, 10 H), 6.03−5.93 (m, 1 H), 5.86−5.76 (m, 1 H), 5.32−5.26 (m, 1 H), 5.20−5.13 (m, 2 H), 5.11−5.07 (m, 1 H), 4.77 (d, 1 H, *J* = 12.2 Hz), 4.63 (d, 1 H *J* = 12.2 Hz), 4.62 (d, 1 H, *J* = 12.1 Hz), 4.50 (d, 1 H, *J* = 12.1 Hz), 4.59 (d, 1 H, *J* = 3.6 Hz), 4.42−4.37 (m, 1 H), 4.30−4.24 (m, 2 H), 4.01−3.95 (m, 1 H), 3.75 (dd, 1 H, *J* = 9.2, 9.4 Hz), 3.70−3.61 (m, 3 H), 3.44 (dd, 1 H, *J* = 3.6, 9.4 Hz), 3.41 (dd, 1 H, *J* = 9.0, 9.2 Hz), 3.35 (s, 3 H); HRMS (FAB) calcd for $C_{27}H_{33}O_6$ $(M - 1)^+$ 453.2277, found 453.2266.

1,6-Di-*O*-acetyl-3,4-di-*O*-allyl-2-*O*-benzyl-D-glucopyranose (21). A mixture of **20** (1.58 g, 3.48 mmol) and concentrated H_2SO_4 (35 μL) in Ac_2O (17.5 mL) was stirred at 0 °C for 3 h. The reaction mixture was poured into EtOH (140 mL), and the resulting solution was stirred at room temperature for 14 h. The solvent was evaporated under reduced pressure, and the residue was partitioned between EtOAc and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/EtOAc 7:2) to give **21** (1.19 g, 79%, as an oil, the α/β ratio was 81:19 on the basis of its ^{1}H NMR spectrum): $[\alpha]^{27}_D$ +60.5 ° (*c* 1.20, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.24 (m, 5 H), 6.26 (d, 0.81 H, *J* = 3.7 Hz), 6.02−5.84 (m, 2 H), 5.56 (d, 0.19 H, *J* = 8.1 Hz), 5.33−5.15 (m, 4 H), 4.77 (d, 0.19 H, *J* = 11.4 Hz), 4.71 (d, 0.19 H, *J* = 11.4 Hz), 4.67 (d, 0.81 H, *J* = 11.6 Hz), 4.63 (d, 0.81 H, *J* = 11.6 Hz), 4.43−4.05 (m, 6 H), 3.86 (ddd, 0.81 H, *J* = 2.5, 3.9, 9.9 Hz), 3.74 (t, 0.81 H, *J* = 9.4 Hz), 3.60−3.51 (m, 0.38 H), 3.55 (dd, 0.81 H, *J* = 3.7, 9.4 Hz), 3.46 (dd, 0.19 H, *J* = 8.1, 9.2 Hz), 3.37 (dd, 0.19 H, *J* = 8.8, 9.8 Hz), 3.36 (dd, 0.81 H, *J* = 9.4, 9.9 Hz), 2.14 (s, 2.43 H), 2.07 (s, 2.43 H), 2.08 (s, 0.57 H), 2.05 (s, 0.57 H); HRMS (FAB) calcd for $C_{23}H_{29}O_8$ $(M - 1)^+$ 433.1861, found 433.1892. Anal. Calcd for $C_{23}H_{30}O_8$: C, 63.58; H, 6.96. Found: C, 63.35; H, 6.94.

6-*O*-Acetyl-3,4-di-*O*-allyl-2-*O*-benzyl-D-glucopyranose (22). A mixture of **21** (1.15 g, 2.65 mmol) and piperidine (13.1 mL, 132 mmol) in THF (26.5 mL) was stirred at room temperature for 36 h. The reaction mixture was diluted with $CHCl_3$ (60 mL), and the resulting solution was washed with aqueous HCl (0.5 M) and saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/EtOAc 2:1) to give **22** (962 mg, 93% as an oil, the α/β ratio was 55:45 on the basis of its ^{1}H NMR spectrum): $[\alpha]^{22}_D$ +36.2 ° (*c* 1.07, $CHCl_3$): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40−7.27 (m, 5 H), 6.02−5.84 (m, 2 H), 5.33−5.14 (m, 4.55 H), 4.90 and 4.76 (each d, each 0.45 H, *J* = 11.1 Hz), 4.77 and 4.67 (each d, each 0.55 H, *J* = 11.8 Hz), 4.69 (dd, 0.45 H, *J* = 5.4, 7.7 Hz), 4.41−4.23 (m, 4.65 H), 4.20 (dd, 0.45 H, *J* = 5.4, 11.9 Hz), 4.11−4.05 (m, 0.90 H), 4.04−4.00 (m, 0.55 H), 3.77 (t, 0.55 H, *J* = 9.3 Hz), 3.52−3.43 (m, 1.45 H), 3.36−3.26 (m, 1.45 H), 3.11 (d, 0.45 H, *J* = 5.3 Hz), 2.88 (d, 0.55 H, *J* = 2.4 Hz), 2.09 (s, 1.35 H, Ac), 2.08 (s, 1.65 H); HRMS (FAB) calcd for $C_{21}H_{29}O_7$ $(M + 1)^+$ 393.1913, found 393.1890. Anal. Calcd for $C_{21}H_{28}O_7$: C, 64.27; H, 7.19. Found: C, 63.98; H, 7.18.

6-*O*-Acetyl-3,4-di-*O*-allyl-2-*O*-benzyl-D-glucopyranosyl Fluoride (23). A mixture of **22** (950 mg, 2.24 mmol) and DAST (0.64 mL, 4.8 mmol) in CH_2Cl_2 (12 mL) was stirred at 0 °C for 2 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL), and the resulting solution was washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/EtOAc 4:1) to give **23** (890 mg, 93% as an oil, the α/β ratio was 27:73 on the basis of its ^{1}H NMR spectrum): $[\alpha]^{21}_D$ +37.4° (*c* 1.60, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.28 (m, 5 H), 6.02−5.83 (m, 2 H), 5.48 (dd, 0.27 H, H-1, *J* = 2.6, 52.9 Hz), 5.33−5.15 (m, 4.73 H),

(24) Kuster, J. M.; Dyong, I. *Liebigs Ann. Chem.* **1975**, 2179−2189.

4.81 and 4.69 (each d, 0.73 H, J = 11.2 Hz), 4.79 and 4.69 (each d, each 0.27 H, J = 12.0 Hz), 4.42−4.06 (m, 5 H), 3.94 (ddd, 0.27 H, J = 2.4, 4.2, 10.2 Hz), 3.79 (t, 0.27 H, J = 9.3 Hz), 3.60 (ddd, 0.73 H, J = 2.2, 5.2, 9.7 Hz), 3.51−3.39 (m, 2.46 H), 3.35 (dd, 0.27 H, J = 9.3, 10.2 Hz), 2.10 (s, 2.19 H, Ac), 2.08 (s, 0.81 H, Ac); HRMS (FAB) calcd for $C_{21}H_{26}FO_6$ 393.1713, found 393.1687.

3-*O*-Allyl-5-*O*-benzyl-1,2-*O*-isopropylidene-α-D-ribofuranose (25). A solution of **24** (876 mg, 3.13 mmol) in THF (10 mL) was added dropwise to a suspension of NaH (60% in mineral oil, 250 mg, 6.25 mmol) in DMF (5 mL) at 0 °C, and the mixture was stirred at the same temperature for 19 h. Allyl bromide (4.33 mL, 50.0 mmol) was added at 0 °C, and the resulting mixture was stirred at room temperature for 3 h. The reaction was quenched with aqueous NH_4Cl (1 M, 25 mL), and the resulting mixture was extracted with EtOAc (50 mL × 2). The organic layer was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue purified by column chromatography (SiO_2, hexane/EtOAc 7:2) to give **25** (928 mg, 93% as an oil): $[\alpha]^{25}_D$ +79.9° (*c* 1.35, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.24 (m, 5 H), 5.95−5.86 (m, 1 H), 5.78 (d, 1 H, J = 3.7 Hz), 5.31−5.25 (m, 1 H), 5.23−5.19 (m, 1 H), 4.64 and 4.55 (each d, each 1 H, J = 12.2 Hz), 4.60 (dd, 1 H J = 3.7, 4.4 Hz), 4.17−4.12 (m, 2 H), 4.08−4.03 (m, 1 H), 3.84 (dd, 1 H, J = 4.4, 9.2 Hz), 3.79 (dd, 1 H, J = 2.0, 11.3 Hz), 3.61 (dd, 1 H, J = 3.9, 11.3 Hz), 1.58 and 1.36 (each s, each 3 H); HRMS (EI) calcd for $C_{18}H_{24}O_5$ 320.1624, found 320.1622. Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.33; H 7.47.

5-*O*-Benzyl-1,2-*O*-isopropylidene-3-*O*-(4-methoxybenzyl)-α-D-ribofuranose (26). Compound **26** (10.8 g, 95% as an oil) was obtained from **24** (412 mg, 0.90 mmol) as described for the synthesis of **25**, with 4-methoxybenzyl chloride (4.64 mL, 115 mmol) instead using allyl bromide: $[\alpha]^{30}_D$ +85.4° (*c* 1.02, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.24 (m, 7 H), 6.88−6.83 (m, 2 H), 5.75 (d, 1 H, J = 3.7 Hz), 4.66 and 4.48 (each d, each 1 H, J = 11.7 Hz), 4.56 and 4.49 (each d, each 1 H, J = 12.3 Hz), 4.53 (dd, 1 H, J = 3.7, 4.4 Hz), 4.16 (ddd, 1 H, J = 2.0, 3.8, 9.1 Hz), 3.84 (dd, 1 H, J = 4.4, 9.1 Hz), 3.79 (s, 3 H), 3.75 (dd, 1 H, J = 2.1, 11.3 Hz), 3.55 (dd, 1 H, J = 3.8, 11.3 Hz), 1.59 and 1.35 (each s, each 3 H); HRMS (EI) calcd for $C_{23}H_{28}O_6$ 400.1886, found 400.1868. Anal. Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 68.83; H, 7.13.

3-*O*-Allyl-5-*O*-benzyl-D-ribitol (27). A solution of **25** in a mixed solution of 1 M HCl and THF (1:1, 140 mL) was heated under reflux for 5.5 h. After being neutralized with $NaHCO_3$ at 0 °C, the mixture was concentrated under reduced pressure (for removing THF), and the resulting solution was extracted with $CHCl_3$ (100 mL × 2). The organic layer was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/EtOAc 1:1) to give 3-*O*-allyl-5-*O*-benzyl-D-ribofuranose (3.85 g, quant as an oil): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.24 (m, 5 H), 5.92−5.83 (m, 1 H), 5.30−5.20 (m, 3 H), 4.66 and 4.58 (each d, each 0.58 H, J = 11.9 Hz), 4.59 and 4.52 (each d, each 0.42 H, J = 12.0 Hz), 4.25−3.91 (m, 5 H, allylic), 3.69 (dd, 0.58 H, J = 3.0, 10.2 Hz), 3.63 (d, 0.42 H, J = 9.8 Hz), 3.59 (dd, 0.58 H, J = 3.0, 10.2 Hz), 3.56 (d, 0.84 H, J = 4.1 Hz), 3.40 (d, 0.58 H, J = 7.4 Hz), 2.87 (d, 0.42 H, J = 7.8 Hz), 2.69 (d, 0.58 H, J = 3.2 Hz); HRMS (FAB) calcd for $C_{15}H_{19}O_5$ $(M - 1)^+$ 279.1232, found 279.1238. Anal. Calcd for $C_{15}H_{20}O_5 \cdot 0.75H_2O$: C, 61.32; H, 7.38. Found: C, 61.70; H, 7.20. A mixture of 3-*O*-allyl-5-*O*-benzyl-D-ribofuranose (3.43 g, 12.3 mmol) and $NaBH_4$ (931 mg, 24.6 mmol) in MeOH (40 mL) was stirred at room temperature for 20 h. After being neutralized with AcOH, the mixture was evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, $CHCl_3$/MeOH, 20:1, 15:1, and 10:1) to give **27** (3.27 g, 95% as an oil): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.27 (m, 5 H), 5.90−5.80 (m, 1 H), 5.26−5.14 (m, 2 H), 4.60 and 4.56 (each d, each 1 H, J = 11.7 Hz), 4.15−4.10 (m, 1 H), 4.06−4.01 (m, 1 H), 3.96 (ddd, 1 H, J = 3.5, 5.4, 7.3 Hz), 3.91−3.86 (m, 1 H), 3.80 (dd, 1 H, J = 4.0, 11.5 Hz), 3.76 (dd, 1 H, J = 4.4, 11.5 Hz), 3.70 (dd, 1 H, J = 3.5, 9.7 Hz), 3.64 (dd, 1 H, J = 5.4, 9.7 Hz), 3.46 (dd, 1 H, J = 6.2, 7.3 Hz), 3.35 (br s, 1 H), 3.09−2.22 (br m, 2 H).

3-*O*-(4-Methoxybenzyl)-5-*O*-benzyl-D-ribitol (28). 5-*O*-Benzyl-3-*O*-(4-methoxybenzyl)-D-ribofuranose (solids, 5.50 g, 81%) was obtained from **26** (5.50 g, 13.8 mmol) as described above for the synthesis of 3-*O*-allyl-5-*O*-benzyl-D-ribofuranose: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.40−7.19 (m, 7 H), 6.92−6.84 (m, 2 H), 5.30−5.20 (m, 1 H), 4.62−4.41 (m, 4 H), 4.29−3.93 (m, 3 H), 3.81 (s, 3 H), 3.65 (d, 0.15 H, J = 9.8 Hz), 3.63 (dd, 0.85 H, J = 3.0, 10.3 Hz), 3.55−3.40 (m, 1.15 H), 3.37 (d, 0.85 H, J = 7.1 Hz), 2.88 (d, 0.15 H, J = 7.5 Hz), 2.68 (d, 0.85 H, J = 3.1 Hz); HRMS (EI) calcd for $C_{20}H_{24}O_6$ 360.1573, found 360.1553. Anal. Calcd for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71. Found: C, 66.44; H, 6.57.

Compound **28** (3.22 g, 91% as an oil) was obtained from 5-*O*-benzyl-3-*O*-(4-methoxybenzyl)-D-ribofuranose (3.50 g, 9.72 mmol) as described above for the synthesis of **27**: $[\alpha]^{27}_D$ +13.6° (*c* 1.24, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.28 (m, 5 H), 7.18−7.15 (m, 2 H), 6.87−6.83 (m, 2 H), 4.58 and 4.53 (each d, each 1 H, J = 11.8 Hz), 4.57 and 4.47 (each d, each 1 H, J = 10.9 Hz), 3.97 (ddd, 1 H, J = 3.4, 5.5. 7.3 Hz), 3.91−3.87 (m, 1 H), 3.81−3.74 (m, 2 H), 3.80 (s, 3 H), 3.68 (dd, 1 H, J = 3.4, 9.6 Hz), 3.60 (dd, 1 H, J = 5.5, 9.6 Hz), 3.56 (dd, 1 H, J = 6.5, 7.3 Hz), 3.45−2.60 (br, 3 H); HRMS (EI) calcd for $C_{20}H_{26}O_6$ 362.1729, found 362.1719. Anal. Calcd for $C_{20}H_{26}O_6 \cdot 1/3H_2O$: C, 65.20; H, 7.30. Found: C, 64.93; H, 7.23.

1,4-Anhydro-3-*O*-allyl-2-*O*-benzoyl-5-*O*-benzyl-D-ribitol (29). A mixture of **27** (3.26 g, 11.6 mmol), Ph_3P (4.56 g, 17.4 mmol), and diethyl azodicarboxylate (2.74 mL, 17.4 mmol) in THF (110 mL) was heated at 60 °C for 42 h. The resulting mixture was evaporated under reduced pressure, and the residue was purified by column chromatography (SiO_2, hexane/EtOAc 2:1) to give crude **13** as an oil, which was contaminated with compounds derived from diethyl azodicarboxylate. A mixture of the obtained oil and BzCl (2.02 mL, 17.4 mmol) in CH_2Cl_2 (20 mL) and pyridine (20 mL) was stirred at room temperature for 2 h. After the reaction was quenched with ice−water, EtOAc (40 mL) and saturated aqueous $NaHCO_3$ (15 mL) were added, and the whole was partitioned. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/EtOAc 7:2) to give **29** (3.04 g, 71% as an oil): $[\alpha]^{25}_D$ +109.3° (*c* 1.14, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10−8.05 (m, 2 H), 7.59−7.54 (m, 1 H), 7.47−7.41 (m, 2 H), 7.38−7.25 (m, 5 H), 5.82−5.73 (m, 1 H), 5.59 (dt, 1 H, J = 2.5, 4.6 Hz), 5.22−5.16 (m, 1 H), 5.12−5.08 (m, 1 H), 4.65 and 4.58 (each d, each 1 H, J = 12.1 Hz), 4.29 (dd, 1 H, J = 4.6, 10.6 Hz), 4.14−4.05 (m, 3 H), 4.05 (dd, 1 H, J = 2.5, 10.6 Hz), 3.99−3.94 (m, 1 H), 3.76 (dd, 1 H, J = 2.5, 10.7 Hz), 3.62 (dd, 1 H, J = 4.2, 10.7 Hz); HRMS (EI) calcd for $C_{22}H_{24}O_5$ 368.1624, found 368.1635. Anal. Calcd for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57. Found: C, 71.54, H, 6.66.

1,4-Anhydro-2-*O*-benzoyl-5-*O*-benzyl-3-*O*-(4-methoxybenzyl)-D-ribitol (30). Compound **30** (4.07 g, 78% as an oil) was obtained from **28** (4.19 g, 11.6 mmol) as described above for the synthesis of **29**: $[\alpha]^{20}_D$ +112.7° (*c* 1.06, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.12−8.06 (m, 2 H), 7.61−7.54 (m, 1 H), 7.48−7.41 (m, 2 H), 7.39−7.28 (m, 5 H), 7.16−7.10 (m, 2 H), 6.78−6.72 (m, 2 H), 5.63−5.57 (m, 1 H), 4.58 and 4.50 (each d, each 1 H, J = 12.1 Hz), 4.58 and 4.38 (each d, each 1 H, J = 11.2 Hz), 4.28 (dd, 1 H, J = 4.6, 10.6 Hz), 4.14−4.08 (m, 2 H), 4.06 (dd, 1 H, J = 2.5, 10.6 Hz), 3.75 (s, 3 H), 3.74−3.66 (m, 1 H), 3.56−3.49 (m, 1 H); MS (EI) *m*/*z* 448 (M^+).

3-*O*-Allyl-1,4-anhydro-5-*O*-benzyl-D-ribitol (13). A mixture of **29** (3.03 g, 8.23 mmol) and NaOMe (28% in MeOH, 0.48 mL, 2.5 mmol) in MeOH (30 mL) was stirred at room temperature for 4 h. After the mixture was neutralized with Dowex 50W resin (×2, H^+ form), the resin was filtered off. The filtrate was evaporated under reduced pressure, and the residue was purified by column chromatography (SiO_2, hexane/EtOAc 2:1) to give **13** (1.77 g, 81% as an oil): $[\alpha]^{24}_D$ +41.7° (*c* 1.15, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.24 (m, 5 H), 5.93−5.84 (m, 1 H), 5.31−5.19 (m, 2 H), 4.62 and 4.55 (each d, each 1 H, J = 12.1 Hz), 4.28−4.23 (m, 1 H), 4.08−4.03 (m,

3 H), 4.00 (ddd, 1 H, J = 3.8, 4.3, 5.9 Hz), 3.91 (dd, 1 H, J = 5.7, 5.9 Hz), 3.79 (dd, 1 H, J = 4.0, 9.7 Hz), 3.64 (dd, 1 H, J = 3.8, 10.5 Hz), 3.57 (dd, 1 H, J = 4.3, 10.5 Hz), 2.66 (d, 1 H, J = 4.9 Hz); HRMS (EI) calcd for $C_{15}H_{20}O_4$ 264.1361, found 264.1385. Anal. Calcd for $C_{15}H_{20}O_4 \cdot 0.2H_2O$: C, 67.24; H, 7.67. Found: C, 67.09; H, 7.31.

1,4-Anhydro-5-*O*-benzyl-3-*O*-(4-methoxybenzyl)-D-ribitol (31). Compound **31** (855 mg, 91% as an oil) was obtained from **30** (1.23 g, 2.75 mmol) as described above for the synthesis of **13**: $[\alpha]^{25}_D$ +40.8 ° (*c* 1.08, $CHCl_3$); ^{1}H NMR (270 MHz, DMSO-d_6) δ 7.40−7.14 (m, 7 H), 6.94−6.80 (m, 2 H), 4.80 (d, 1 H, J = 5.3 Hz), 4.60 and 4.37 (each d, each 1 H, J = 11.4 Hz), 4.49 and 4.43 (each d, each 1 H, J = 12.2 Hz), 4.23−4.12 (m, 1 H), 3.92−3.80 (m, 1 H), 3.86 (dd, 1 H, J = 4.6, 9.2 Hz), 3.73 (s, 3 H), 3.70 (dd, 1 H, J = 4.6, 6.9 Hz), 3.58 (dd, 1 H, J = 3.3, 9.2 Hz), 3.52 (dd, 1 H, J = 3.1, 10.7 Hz), 3.41 (dd, 1 H, J = 5.1, 10.7 Hz); HRMS (EI) calcd for $C_{20}H_{24}O_5$ 344.1624, found 344.1616. Anal. Calcd for $C_{20}H_{24}O_5 \cdot 0.2H_2O$: C, 69.03; H, 7.07. Found: C, 69.08; H, 7.05.

1,4-Anhydro-2,5-di-*O*-benzyl-3-*O*-(4-methoxybenzyl)-D-ribitol (32). A mixture of **31** (812 mg, 2.36 mmol) and NaH (60% in mineral oil, 283 mg, 7.08 mmol) in DMF (12 mL) was stirred at room temperature for 2 h. BnBr (0.337 mL, 2.83 mmol) was added, and the resulting mixture was stirred at room temperature for 2 h. After the reaction was quenched with aqueous NH_4Cl (1 M, 20 mL), EtOAc (40 mL) and H_2O (10 mL) were added to the mixture, and then the whole was partitioned. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/EtOAc 3:1) to give **32** (900 mg, 88% as an oil): $[\alpha]^{31}_D$ +49.8° (*c* 1.08, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.24 (m, 10 H), 7.23−7.19 (m, 2 H), 6.85−6.80 (m, 2 H), 4.60 and 4.58 (each d, each 1 H, J = 12.8 Hz), 4.57 and 4.45 (each d, each 1 H, J = 11.6 Hz), 4.56 and 4.49 (each d, each 1 H, J = 12.1 Hz), 4.15−4.11 (m, 1 H), 4.02−3.96 (m, 2 H), 3.93 (dd, 1 H, J = 3.7, 8.8 Hz), 3.91 (dd, 1 H, J = 5.0, 6.1 Hz), 3.79 (s, 3 H), 3.61 (dd, 1 H, J = 3.3, 10.7 Hz), 3.50 (dd, 1 H, J = 4.4, 10.7 Hz); HRMS calcd for $C_{27}H_{30}O_5$ 434.2093, found 434.2122.

2-*O*-Allyl-1,4-anhydro-5-*O*-benzyl-3-*O*-(4-methoxybenzyl)-D-ribitol (33). Compound **33** (1.33 g, 90% as an oil) was obtained from **31** (1.32 g, 3.84 mmol) as described above for the synthesis of **32**, with allyl bromide (0.399 mL, 4.61 mmol): $[\alpha]^{21}_D$ +53.0° (*c* 1.02, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.39−7.19 (m, 7 H), 6.89−6.79 (m, 2 H), 6.01−5.84 (m, 1 H), 5.33−5.14 (m, 2 H), 4.59 and 4.48 (each d, each 1 H, J = 11.5 Hz), 4.57 and 4.49 (each d, each 1 H, J = 12.2 Hz), 4.14−3.85 (m, 7 H), 3.80 (s, 3 H), 3.61 (dd, 1 H, J = 3.3, 10.6 Hz), 3.49 (dd, 1 H, J = 4.3, 10.6 Hz); HRMS (EI) calcd for $C_{23}H_{28}O_5$ 384.1937, found 384.1921. Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 71.74; H, 7.41.

2-*O*-Allyl-1,4-anhydro-5-*O*-benzyl-D-ribitol (11). A mixture of **33** (1.02 g, 2.26 mmol), DDQ (725 mg, 3.19 mmol), and H_2O (0.5 mL) in CH_2Cl_2 (9 mL) was stirred at room temperature for 34 h. After addition of saturated aqueous $NaHCO_3$ (20 mL), the mixture was extracted with CH_2Cl_2 (15 mL × 2). The organic layer was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/EtOAc 3:1) to give **11** (596 mg, 85% as an oil): $[\alpha]^{26}_D$ +56.7 ° (*c* 1.04, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.24 (m, 5 H), 5.96−5.87 (m, 1 H), 5.33−5.27 (m, 1 H), 5.25−5.21 (m, 1 H), 4.59 and 4.56 (each d, each 1 H, J = 12.2 Hz), 4.14−3.99 (m, 5 H), 3.91 (dt-like ddd, 1 H, J = 3.1, 5.0, 5.3 Hz), 3.82 (dd, 1 H, J = 4.2, 9.7 Hz), 3.69 (dd, 1 H, J = 3.1, 10.6 Hz), 3.58 (dd, 1 H, J = 5.0, 10.6 Hz), 2.68 (d, 1 H, J = 7.1 Hz); HRMS (EI) calcd for $C_{15}H_{20}O_4$ 264.1361, found 264.1356. Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.93; H, 7.55.

1,4-Anhydro-2,5-di-*O*-benzyl-D-ribitol (12). Compound **12** (541 mg, 90% as a solid) was obtained from **32** (835 mg, 1.92 mmol) as described above for the synthesis of **11**: $[\alpha]^{27}_D$ +50.5° (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.24 (m, 10 H), 4.64 and 4.58 (each d, each 1 H, J = 11.7 Hz), 4.59 and 4.55 (each d, each 1 H, J = 12.1 Hz), 4.11−4.04 (m, 3 H), 3.93 (ddd, 1 H, J = 3.1, 5.1, 5.2 Hz), 3.88−3.83 (m, 1 H), 3.68 (dd, 1 H, J = 3.1, 10.6 Hz), 3.57 (dd, 1 H, J = 5.1, 10.6 Hz), 2.69 (d, 1 H, J = 6.9 Hz); HRMS (EI) calcd for $C_{19}H_{22}O_4$ 314.1518, found 314.1534. Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.57; H, 7.20.

3,4-*O*-Isopropylidene-1-*O*-trityl-D-erythritol (35). A solution of **34** (16.7 g, 98.3 mmol) in Et_2O (100 mL) was added dropwise to a suspension of $LiAlH_4$ (4.46 g, 118 mmol) in Et_2O (96 mL) at 0 °C. The mixture was stirred at room temperature for 4 h and then heated under reflux for 1 h. Water (4.9 mL) and aqueous NaOH (15%) were added, and the resulting mixture was stirred at room temperature for 24 h. The resulting precipitates were filtered off with Celite and washed with hot EtOAc. The filtrate and washings were combined and evaporated under reduced pressure, and the residue was coevaporated with toluene (×3) and pyridine (×3). A mixture of the resulting residue and TrCl (30.1 g, 108 mmol) in pyridine (200 mL) was heated at 70 °C for 23 h. The resulting mixture was evaporated under reduced pressure, and the residue was partitioned between Et_2O (300 mL) and H_2O (150 mL). The aqueous layer was extracted with Et_2O (300 mL). The organic layer was combined, washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/EtOAc 5:1) to give **35** (25.9 g, 65% as a syrup): $[\alpha]^{25}_D$ −2.2° (*c* 1.52, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45−7.41 (m, 6 H), 7.32−7.27 (m, 6 H), 7.26−7.22 (m, 3 H), 4.09 (dt, 1 H, J = 6.2, 6.3 Hz), 4.00 (dd, 1 H, J = 6.3, 8.4 Hz), 3.94 (dd, 1 H, J = 6.2, 8.4 Hz), 3.78 (ddt, 1 H, J = 4.0, 6.0, 6.2 Hz), 3.32 (dd, 1 H, J = 4.0, 9.8 Hz), 3.26 (dd, 1 H, J = 6.0, 9.8 Hz), 2.33 (d, 1 H, J = 4.0 Hz), 1.35 and 1.33 (each s, each 3 H); HRMS (EI) calcd for $C_{26}H_{28}O_4$ 404.1986, found 404.2000.

2-*O*-Allyl-3,4-*O*-isopropylidene-1-*O*-trityl-D-erythritol (36). Compound **36** (5.07 g, 57% as a syrup) was obtained from **35** (8.08 g, 20.0 mmol) as described above for the synthesis of **25**: $[\alpha]^{23}_D$ +10.7 ° (*c* 1.12, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49−7.41 (m, 6 H), 7.33−7.20 (m, 9 H), 5.95−5.86 (m, 1 H), 5.29−5.22 (m, 1 H), 5.18−5.13 (m, 1 H), 4.24−4.18 (m, 1 H), 4.14 (ddd, 1 H, J = 5.7, 6.4, 6.6 Hz), 4.12−4.07 (m, 1 H), 4.01 (dd, 1 H, J = 6.4, 8.2 Hz), 3.97 (dd, 1 H, J = 6.6, 8.2 Hz), 3.59 (ddd, 1 H, J = 3.5, 5.3, 5.7 Hz), 3.30 (dd, 1 H, J = 3.5, 10.2 Hz), 3.16 (dd, 1 H, J = 5.3, 10.2 Hz), 1.36 and 1.32 (each s, each 3 H); HRMS (EI) calcd for $C_{28}H_{29}O_4$ 429.2064 $(M - CH_3)^+$, found 429.2054.

2-*O*-Allyl-D-erythritol (37). A mixture of **36** (898 mg, 2.02 mmol) and *p*-TsOH·H_2O (115 mg, 0.605 mmol) in MeOH (10 mL) was stirred at room temperature for 4 days. The mixture was evaporated under reduced pressure, and the residue was purified by column chromatography (SiO_2, $CHCl_3$/EtOH 9:1) to give **37** (164 mg, 50% as an oil): ^{1}H NMR (270 MHz, DMSO-d_6) δ 6.04−5.89 (m, 1 H), 5.36−5.13 (m, 2 H), 4.66 (d, 1 H, J = 5.1 Hz), 4.51 (t, 1 H, J = 5.7 Hz), 4.47 (t, 1 H, J = 5.7 Hz), 4.24−4.03 (m, 2 H), 3.74−3.30 (m, 6 H); HRMS (EI) calcd for $C_7H_{14}O_4$ 162.0891, found 162.0879.

2-*O*-Allyl-1,4-anhydro-D-erythritol (14). Trifluoromethanesulfonyl anhydride (2.03 mL, 12.1 mmol) was added to a solution of **37** (1.95 g, 12.0 mmol), Et_3N (3.36 mL, 24.1 mmol), and DMAP (147 mg, 1.20 mmol) in MeCN (40 mL) at room temperature, and the mixture was stirred at the same temperature for 3 days. The reaction was quenched with H_2O, and the resulting mixture was evaporated under reduced pressure. The residue was partitioned between $CHCl_3$ and saturated aqueous $NaHCO_3$, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/EtOAc 1:1) to give **14** (792 mg, 41% as an oil): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.97−5.88 (m, 1 H), 5.35−5.22 (m, 2 H), 4.29−4.25 (m, 1 H), 4.11−4.08 (m, 2 H), 4.02 (ddd, 1 H, J = 5.2, 5.6, 6.2 Hz), 3.93 (dd, 1 H, J = 6.2, 9.5 Hz), 3.90 (dd, 1 H, J = 5.0, 9.7 Hz), 3.77 (dd, 1 H, J = 5.2, 9.5 Hz), 3.75 (dd, 1 H, J = 3.9, 9.7 Hz), 2.73 (br, 1 H); HRMS (EI) calcd for $C_7H_{12}O_3$ 144.0786, found 144.0778.

General Procedure for Glycosidation Reactions with Glycosyl Donor 23. TMSOTf (86 μL, 0.445 mmol) was added to a solution of **23** (96 mg, 0.244 mmol), Et_3N (31 μL, 0.222 mmol), and a glycosyl acceptor (0.222 mmol) in a solvent (4

mL) at room temperature, and the mixture was stirred at the same temperature for several hours (indicated in Table 1). The reaction mixture was diluted with EtOAc (20 mL) and then washed with H_2O, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/EtOAc 4:1 or 2:1) to give the corresponding glycosidation product in the yield shown in Table 1.

Cyclopentyl 6-*O*-acetyl-3,4-di-*O*-allyl-2-*O*-benzyl-D-glucopyranoside (38): entry 5 in Table 1, the α/β ratio was 77:23 based on its ^{1}H NMR spectrum; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.28 (m, 5 H), 6.05−5.82 (m, 2 H), 5.33−5.14 (m, 4 H), 4.87 and 4.66 (each d, each 0.23 H, J = 10.9 Hz), 4.78 (d, 0.77 H, J = 3.6 Hz), 4.72 and 4.60 (each d, each 0.77 H, J = 11.9 Hz), 4.57−4.19 (m, 5.23 H), 4.13−4.03 (m, 2 H), 3.85−3.72 (m, 1.77 H), 3.46−3.24 (m, 2.23 H), 2.08 (s, 0.69 H), 2.07 (s, 2.31 H), 1.83−1.52 (m, 8 H); HRMS (FAB) calcd for $C_{26}H_{37}O_7$ 461.2539 $(M + 1)^+$, found 461.2514.

(2*R*,3*S*,4*S*)-4-(Allyloxy)-2-(benzyloxymethyl)tetrahydrofuran-3-yl 6-*O*-acetyl-3,4-di-*O*-allyl-2-*O*-benzyl-α-D-glucopyranoside (39): containing 5% of the β-anomer; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.24 (m, 10 H), 6.01−5.81 (m, 3 H), 5.31−5.20 (m, 3 H), 5.19−5.11 (m, 3 H), 5.16 (d, 1 H, J = 3.5 Hz), 4.76 and 4.61 (each d, each 1 H, J = 11.9 Hz), 4.58 and 4.52 (each d, each 1 H, J = 12.1 Hz), 4.44−4.38 (m, 1 H), 4.33−4.28 (m, 1 H), 4.27−4.01 (m, 10 H), 3.91−3.86 (m, 1 H), 3.79 (dd, 1 H, J = 9.3, 9.6 Hz), 3.72 (ddd, 1 H, J = 2.2, 4.5, 9.8 Hz), 3.62 (dd, 1 H, J = 3.3, 10.7 Hz), 3.57 (dd, 1 H, J = 4.0, 10.7 Hz), 3.45 (dd, 1 H, J = 3.5, 9.6 Hz), 3.28 (dd, 1 H, J = 9.3, 9.8 Hz), 2.02 (s, 3 H); HRMS (FAB) calcd for $C_{36}H_{45}O_{10}$ 637.3012 $(M - 1)^+$, found 637.3057.

(2*R*,3*S*,4*S*)-4-(Benzyloxy)-2-(benzyloxymethyl)tetrahydrofuran-3-yl 6-*O*-acetyl-3,4-di-*O*-allyl-2-*O*-benzyl-α-D-glucopyranoside (40): containing 7% of the β-anomer; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.16 (m, 15 H), 5.99−5.83 (m, 2 H), 5.29−5.09 (m, 5 H), 5.66 and 4.56 (each d, each 1 H, J = 11.7 Hz), 4.62 and 4.49 (each d, each 1 H, J = 11.9 Hz), 4.58 and 4.52 (each d, each 1 H, J = 12.1 Hz), 4.39−4.33 (m, 1 H), 4.32−4.27 (m, 1 H, allylic), 4.24−4.02 (m, 7 H), 4.02 (dd, 1 H J = 5.4, 9.1 Hz), 3.90 (dd, 1 H, J = 5.8, 9.1 Hz), 3.78 (dd, 1 H, J = 9.2, 9.5 Hz), 3.74 (ddd, 1 H, J = 2.0, 4.5, 10.0 Hz), 3.62 (dd, 1 H, J = 3.4, 10.7 Hz), 3.58 (dd, 1 H, J = 4.2, 10.7 Hz), 3.42 (dd, 1 H, J = 3.6, 9.5 Hz), 3.27 (dd, 1 H, J = 9.2, 10.0 Hz), 2.02 (s, 3 H); HRMS (FAB) calcd for $C_{40}H_{49}O_{10}$ 689.3325 $(M + 1)^+$, found 689.3290.

(2*R*,3*R*,4*S*)-3-(Allyloxy)-2-(benzyloxymethyl)tetrahydrofuran-4-yl 6-*O*-acetyl-3,4-di-*O*-allyl-2-*O*-benzyl-α-D-glucopyranoside (41): containing 15% of the β-anomer; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.23 (m, 10 H), 6.01−5.82 (m, 3 H), 5.32−5.08 (m, 6 H), 4.74 and 4.59 (each d, each 1 H, J = 11.9 Hz), 4.74 (d, 1 H, J = 3.6 Hz), 4.61 and 4.54 (each d, each 1 H, J = 12.0 Hz), 4.41−4.36 (m, 1 H), 4.34−4.23 (m, 3 H), 4.20−4.02 (m, 6 H), 4.02−3.95 (m, 2 H), 3.92−3.86 (m, 2 H), 3.81 (dd, 1 H, J = 9.3, 9.4 Hz), 3.65 (dd, 1 H, J = 3.2, 10.6 Hz), 3.55 (dd, 1 H, J = 4.2, 10.6 Hz), 3.41 (dd, 1 H, J = 3.6, 9.4 Hz), 3.29 (dd, 1 H, J = 9.3, 9.6 Hz), 2.05 (s, 3 H); HRMS (FAB) calcd for $C_{36}H_{45}O_{10}$ 637.3012 $(M - 1)^+$, found 637.3008.

(3*S*,4*R*)-3-(Allyloxy)tetrahydrofuran-4-yl 6-*O*-acetyl-3,4-di-*O*-allyl-2-*O*-benzyl-α-D-glucopyranoside (42): containing 6% of the β-anomer; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.24 (m, 5 H), 6.01−5.83 (m, 3 H), 5.31−5.22 (m, 3 H), 5.19−5.12 (m, 3 H), 5.08 (d, 1 H, H-1), 4.72 and 4.68 (each d, each 1 H, J = 11.9 Hz), 4.43−4.38 (m, 1 H), 4.35−4.30 (m, 1 H), 4.28−4.18 (m, 4 H, allylic), 4.14 (m, 1 H), 4.09−4.02 (m, 3 H), 3.98 (dd, 1 H, J = 5.8, 9.2 Hz), 3.96 (dd, 1 H, J = 5.8, 9.2 Hz), 3.84−3.75 (m, 4 H), 3.45 (dd, 1 H, J = 3.6, 9.7 Hz), 3.29−3.24 (dd, 1 H), 2.08 (s, 3 H); HRMS (FAB) calcd for $C_{28}H_{37}O_9$ 517.2437 $(M - 1)^+$, found 517.2463.

(2*R*,3*S*,4*S*)-4-(Allyloxy)-2-(benzyloxymethyl)tetrahydrofuran-3-yl 3,4-Di-*O*-allyl-2,6-di-*O*-benzyl-α-D-glucopyranoside (15). A mixture of **39** (1.48 g, 2.32 mmol) and NaOMe (28% in MeOH, 0.695 mL, 3.60 mmol) in MeOH (12 mL) was stirred at room temperature for 6 h. After the mixture was neutralized with Dowex 50W resin (×2, H^+ form), the resin was filtered off. The filtrate was evaporated under reduced pressure, and the residue was coevaporated with toluene (×3). A mixture of the resulting residue and NaH (60% in mineral oil, 278 mg, 6.95 mmol) in DMF (12 mL) was stirred at room temperature for 1 h. BnBr (0.331 mL, 2.78 mmol) was added, and the resulting mixture was stirred at room temperature for 12 h. After the reaction was quenched with aqueous NH_4Cl (1 M, 20 mL), the resulting mixture was extracted with Et_2O (60 mL). The organic layer was washed with brine (20 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/EtOAc 3:1) to give **15** (1.53 mg, 96% as an oil, containing a trace amount of the β-anomer): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.22 (m, 15 H), 6.01−5.75 (m, 3 H), 5.29−5.06 (m, 7 H, H-1), 4.75 and 4.62 (each d, each 1 H, J = 11.9 Hz), 4.56 and 4.40 (each d, each 1 H, J = 12.0 Hz), 4.53 and 4.47 (each d, each 1 H, J = 12.0 Hz), 4.42−4.36 (m, 1 H), 4.28−4.19 (m, 3 H), 4.17−4.13 (m, 1 H), 4.13−3.99 (m, 4 H), 3.98−3.93 (m, 1 H), 3.89 (dd, 1 H, J = 4.9, 8.7 Hz), 3.76 (t, 1 H, J = 9.3 Hz), 3.64−3.58 (m, 2 H), 3.56 (dd, 1 H, J = 3.5, 10.6 Hz), 3.55 (dd, 1 H, J = 4.3, 10.6 Hz), 3.49−3.43 (m, 2 H), 3.42 (dd, 1 H, J = 9.3, 9.7 Hz); HRMS (FAB) calcd for $C_{41}H_{49}O_9$ 685.3376 $(M - 1)^+$, found 685.3386.

(2*R*,3*S*,4*S*)-4-(Benzyloxy)-2-(benzyloxymethyl)tetrahydrofuran-3-yl 3,4-Di-*O*-allyl-2,6-di-*O*-benzyl-α-D-glucopyranoside (43). Compound **43** (488 mg, 92% as an oil, containing a trace amount of the β-anomer) was obtained from **40** (494 mg, 0.718 mmol) as described above for the synthesis of **15**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.16 (m, 20 H), 5.99−5.89 (m, 1 H), 5.85−5.75 (m, 1 H), 5.27−5.06 (m, 5 H), 4.67 and 4.56 (each d, each 1 H, J = 11.8 Hz), 4.61 and 4.50 (each d, each 1 H, J = 11.8 Hz), 4.57 and 4.40 (each d, each 1 H, J = 12.1 Hz), 4.52 and 4.47 (each d, each 1 H, J = 12.0 Hz), 4.38−4.32 (m, 1 H), 4.27−4.16 (m, 4 H), 4.12−4.08 (m, 1 H), 4.00 (dd, 1 H, J = 5.2, 9.1 Hz), 3.97−3.92 (m, 1 H), 3.90 (dd, 1 H, J = 5.5, 9.1 Hz), 3.76 (m, 1 H), 3.67−3.53 (m, 4 H), 3.49−3.39 (m, 3 H); HRMS (FAB) calcd for $C_{45}H_{53}O_9$ 737.3689 $(M + 1)^+$, found 737.3726.

(3*S*,4*R*)-3-(Allyloxy)tetrahydrofuran-4-yl 3,4-Di-*O*-allyl-2,6-di-*O*-benzyl-α-D-glucopyranoside (44). Compound **44** (1.76 g, 94% as an oil) was obtained from **42** (1.72 g, 3.32 mmol) as described above for the synthesis of **15**: $[\alpha]^{27}_D$ +58.0 ° (*c* 1.06, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.23 (m, 10 H), 6.00−5.77 (m, 3 H), 5.30−5.06 (m, 6 H), 5.10 (d, 1 H, J = 3.6 Hz), 4.71 and 4.67 (each d, each 1 H, J = 12.0 Hz), 4.62 and 4.49 (each d, each 1 H, J = 12.1 Hz), 4.41−4.13 (m, 6 H), 4.08−3.92 (m, 5 H), 3.83−3.76 (m, 3 H), 3.71−3.66 (m, 1 H), 3.64−3.59 (m, 1 H), 3.46 (dd, 1 H, J = 3.6, 9.6 Hz), 3.41 (t, 1 H, J = 9.2 Hz); HRMS (FAB) calcd for $C_{33}H_{43}O_8$ 567.2958 $(M + 1)^+$, found 567.2985.

(2*R*,3*R*,4*S*)-3-(Allyloxy)-2-(benzyloxymethyl)tetrahydrofuran-4-yl 3,4-Di-*O*-allyl-2,6-di-*O*-benzyl-α-D-glucopyranoside (51). Compound **51** (477 mg, 65% as an oil) was obtained from **41** (678 mg, 1.06 mmol) as described above for the synthesis of **15**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40−7.22 (m, 15 H), 6.02−5.76 (m, 3 H), 5.31−5.04 (m, 6 H), 4.77 (d, 1 H, J = 3.5 Hz), 4.75 (d, 1 H, J = 12.2 Hz), 4.65−4.57 (m, 3 H), 4.54 (d, 1 H, J = 12.1 Hz), 4.49 (d, 1 H, J = 12.0 Hz), 4.40−4.34 (m, 1 H), 4.30−4.23 (m, 2 H), 4.21−4.17 (m, 1 H), 4.13−4.07 (m, 2 H), 4.02−3.84 (m, 6 H), 3.79 (t, 1 H, J = 9.3 Hz), 3.68−3.62 (m, 2 H), 3.61−3.57 (m, 1 H), 3.54 (dd, 1 H, J = 4.4, 10.6 Hz), 3.46−3.40 (m, 2 H); HRMS (FAB) calcd for $C_{41}H_{51}O_9$ 687.3533 $(M + 1)^+$, found 687.3503.

(2*R*,3*R*,4*S*)-4-Acetoxy-2-(benzyloxymethyl)tetrahydrofuran-3-yl 3,4-Di-*O*-acetyl-2,6-di-*O*-benzyl-α-D-glucopyranoside (45). A mixture of **15** (1.51 g, 2.20 mmol), Pd−C (10%, 211 mg), and *p*-TsOH·H_2O (206 mg, 1.08 mmol) in EtOH (15 mL) and H_2O (3 mL) was heated under reflux for 4 h. The insoluble materials were filtered off, and the filtrate was evaporated under reduced pressure. After the residue was coevaporated with pyridine (×3), a mixture of the resulting residue and Ac_2O (0.747 mL, 7.92 mmol) in pyridine (11 mL) was stirred at room temperature for 15 h. After the reaction was quenched with ice−water, the resulting mixture was evaporated under reduced pressure, and the residue was

partitioned between EtOAc (35 mL) and H_2O (10 mL). The organic layer was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/EtOAc 3:1) to give **45** (1.49 g, 98% as an oil): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.18 (m, 15 H), 5.40 (dd, 1 H, J = 9.8, 9.9 Hz), 5.37−5.33 (m, 1 H), 5.04 (dd, 1 H, H-4, J = 9.8, 10.0 Hz), 5.03 (d, 1 H, J = 3.5 Hz), 4.66 and 4.49 (each d, each 1 H, J = 12.2 Hz), 4.54 and 4.49 (each d, each 1 H, J = 12.1 Hz), 4.51 and 4.31 (each d, each 1 H, J = 12.1 Hz), 4.37 (dd, 1 H, J = 5.5, 6.5 Hz), 4.18−4.15 (m, 1 H), 4.16 (dd, 1 H, J = 4.9, 10.1 Hz), 3.90 (dd, 1 H, J = 3.6, 10.1 Hz), 3.89−3.84 (m, 1 H), 3.69 (dd, 1 H, J = 2.8, 11.0 Hz), 3.61 (dd, 1 H, J = 3.9, 11.0 Hz), 3.55 (dd, 1 H, J = 3.5, 9.9 Hz), 3.33 (dd, 1 H, J = 2.5, 10.8 Hz), 3.29 (dd, 1 H, J = 4.0, 10.8 Hz), 1.94, 1.89, and 1.88 (each s, each 3 H); HRMS (EI) calcd for $C_{38}H_{44}O_{12}$ 692.2830, found 692.2841.

(2*R*,3*S*,4*S*)-4-(Benzyloxy)-2-(benzyloxymethyl)tetrahydrofuran-3-yl 3,4-Di-*O*-acetyl-2,6-di-*O*-benzyl-D-glucopyranoside (46). Compound **46** (261 mg, 55% as an oil) was obtained from **43** (470 mg, 0.685 mmol) as described above for the synthesis of **45**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.18 (m, 18 H), 7.12−7.07 (m, 2 H), 5.43 (dd, 1 H, J = 9.7, 9.8 Hz), 5.29 (d, 1 H, J = 3.6 Hz), 5.05 (dd, 1 H, J = 9.7, 10.0 Hz), 4.65 and 4.57 (each d, each 1 H, J = 11.8 Hz), 4.56 and 4.37 (each d, each 1 H, J = 12.4 Hz), 4.53 and 4.47 (each d, each 1 H, J = 12.1 Hz), 4.52 and 4.33 (each d, each 1 H, J = 12.2 Hz), 4.29 (t, 1 H, J = 5.0 Hz), 4.21 (dt, 1 H, J = 4.0, 5.0 Hz), 4.11 (ddd, 1 H, J = 5.0, 5.4, 6.1 Hz), 4.01 (dd, 1 H, J = 5.4, 8.9 Hz), 3.90 (dd, 1 H, J = 6.1, 8.9 Hz), 3.86 (ddd, 1 H, J = 2.5, 4.0, 10.0 Hz), 3.59 (d, 2 H, J = 4.0 Hz), 3.56 (dd, 1 H, J = 3.6, 9.8 Hz), 3.34 (dd, 1 H, J = 2.5, 10.8 Hz), 3.28 (dd, 1 H, J = 4.0, 10.8 Hz), 1.98 and 1.88 (each s, each 3 H); HRMS (FAB) calcd for $C_{43}H_{49}O_{11}$ $(M + 1)^+$, 741.3274, found 741.3247.

(3*S*,4*R*)-3-Acetoxytetrahydrofuran-4-yl 3,4-Di-*O*-acetyl-2,6-di-*O*-benzyl-α-D-glucopyranoside (47). Compound **47** (350 mg, 77% as an oil) was obtained from **44** (451 mg, 0.613 mmol) as described above for the synthesis of **45**: $[\alpha]^{23}_D$ +58.1° (*c* 1.23, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.24 (m, 10 H), 5.41 (t-like dd, 1 H, J = 9.8, 9.9 Hz), 5.28−5.24 (m, 1 H), 5.10 (t-like dd, 1 H, J = 9.8, 9.9 Hz), 4.98 (d, 1 H, J = 3.6 Hz), 4.65 and 4.50 (each d, each 1 H, J = 12.2 Hz), 4.57 and 4.45 (each d, each 1 H, J = 12.1 Hz), 4.35−4.31 (m, 1 H), 4.05 (dd, 1 H, J = 5.9, 10.1 Hz), 3.95 (dd, 1 H, J = 6.0, 9.4 Hz), 3.93−3.84 (m, 3 H), 3.54 (dd, 1 H, J = 3.6, 9.9 Hz), 3.48 (dd, 1 H, J = 2.9, 10.7 Hz), 3.45 (dd, 1 H, J = 4.5, 10.7 Hz), 1.96, 1.92, and 1.90 (each s, each 3 H); HRMS (FAB) calcd for $C_{30}H_{37}O_{11}$ 573.2335 $(M + 1)^+$, found 573.2357.

(2*R*,3*R*,4*S*)-3-Acetoxy-2-(benzyloxymethyl)tetrahydrofuran-4-yl 3,4-Di-*O*-acetyl-2,6-di-*O*-benzyl-α-D-glucopyranoside (52). Compound **52** (1.35 g, 77% as an oil) was obtained from **51** (1.73 g, 3.06 mmol) as described above for the synthesis of **45**: $[\alpha]^{30}_D$ +114.8° (*c* 1.01, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.22 (m, 15 H), 5.37 (dd, 1 H, J = 9.9, 9.7 Hz), 5.09 (t, 1 H, J = 5.7 Hz), 5.08 (dd, 1 H, J = 9.7, 9.8 Hz), 4.74 (d, 1 H, J = 3.5 Hz), 4.63 and 4.51 (each d, each 1 H, J = 12.3 Hz), 4.58 and 4.53 (each d, each 1 H, J = 12.1 Hz), 4.57 and 4.40 (each d, each 1 H, J = 12.1 Hz), 4.43−4.38 (m, 1 H), 4.17−4.15 (m, 1 H), 4.09 (dd, 1 H, J = 5.6, 9.4 Hz), 3.91 (ddd, 1 H, J = 2.7, 3.7, 9.8 Hz), 3.80 (dd, 1 H, J = 5.5, 9.4 Hz), 3.64 (dd, 1 H, J = 3.0, 10.7 Hz), 3.56 (dd, 1 H, J = 4.1, 10.7 Hz), 3.56 (dd, 1 H, J = 3.5, 9.9 Hz), 3.45 (dd, 1 H, J = 2.7, 10.8 Hz), 3.41 (dd, 1 H, J = 3.7, 10.8 Hz), 2.12, 2.00, and 1.88 (each s, each 3 H); HRMS (FAB) calcd for $C_{38}H_{43}O_{12}$ 691.2754 $(M - 1)^+$, found 691.2745.

(2*R*,3*R*,4*S*)-2-(Benzyloxymethyl)-4-hydroxytetrahydrofuran-3-yl 2,6-Di-*O*-benzyl-α-D-glucopyranoside 3,4,4′-Tris(dibenzyl phosphate) (48). A mixture of **45** (1.38 g, 2.32 mmol) and NaOMe (28% in MeOH, 0.115 mL, 0.597 mmol) in MeOH (10 mL) was stirred at room temperature for 4 h. After the mixture was neutralized with Dowex 50W resin (×2, H^+ form), the resin was filtered off. The filtrate was evaporated under reduced pressure, and the residue was coevaporated with benzene (×3). A mixture of the resulting residue, tetrazole (976 mg, 13.9 mmol), and dibenzyl(diisopropyl)-phosphoroamidite (3.01 mL, 8.96 mmol) in CH_2Cl_2 (35 mL) was stirred at room temperature for 7 h. After the reaction was quenched with H_2O (0.3 mL), *m*-CPBA (3.00 g, 13.9 mmol) was added at −40 °C. The resulting mixture was stirred at room temperature for 2 h, aqueous Na_2SO_3 (10%, 50 mL) and EtOAc (50 mL) were added, and then the whole was partitioned. The organic layer was washed with aqueous saturated $NaHCO_3$, H_2O, and brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, $CHCl_3/Et_2O$ 3:1) to give **48** (1.98 g, 74% as an oil): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.02 (m, 45 H), 5.26 (d, 1 H, J = 3.6 Hz), 5.02−4.82 (m, 13 H, H-2′ benzylic), 4.75−4.69 (m, 1 H), 4.73 and 4.45 (each d, each 1 H, J = 11.6 Hz), 4.58 (m, 1 H), 4.46 and 4.39 (each d, each 1 H, J = 11.9 Hz), 4.41 and 4.30 (each d, each 1 H, J = 11.9 Hz), 4.24−4.20 (m, 1 H), 4.14−4.10 (m, 1 H), 3.99−3.93 (m, 2 H), 3.80−3.75 (m, 1 H), 3.64 (dd, 1 H, J = 4.4, 11.0 Hz), 3.60−3.55 (m, 2 H), 3.52 (dd, 1 H, J = 3.6, 10.9 Hz), 3.50 (dd, 1 H, J = 3.8, 10.9 Hz); ^{31}P NMR (125 MHz, $CDCl_3$) δ −0.57, −1.70, −1.87; HRMS (FAB) calcd for $C_{74}H_{78}O_{18}P_3$ 1347.4401 $(M - 1)^+$, found 1347.4480.

(2*R*,3*S*,4*S*)-4-(Benzyloxy)-2-(benzyloxymethyl)tetrahydrofuran-3-yl 2,6-Di-*O*-benzyl-α-D-glucopyranoside 3,4-Bis(dibenzyl phosphate) (49). Compound **49** (371 mg, 68% as an oil) was obtained from **46** (349 mg, 0.472 mmol) as described above for the synthesis of **48**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29−7.15 (m, 40 H), 5.33 (d, 1 H, J = 3.5 Hz), 5.11−4.76 (m, 9 H), 4.65−4.55 (m, 3 H), 4.50−4.38 (m, 5 H), 4.31 (d, 1 H, J = 11.8 Hz), 4.24 (t, 1 H, J = 4.6 Hz), 4.19−4.15 (m, 1 H), 4.11−4.05 (m, 1 H), 3.97 (dd, 1 H, J = 5.4, 8.8 Hz), 3.87 (dd, 1 H, J = 6.6, 8.8 Hz), 3.85−3.80 (m, 1 H), 3.67 (dd, 1 H, J = 4.4, 10.8 Hz), 3.62−3.49 (m, 5 H); ^{31}P NMR (125 MHz, $CDCl_3$) δ −1.73, −1.93; HRMS (FAB) calcd for $C_{67}H_{71}O_{15}P_2$ 1177.4268, found 1177.4220.

(3*S*,4*R*)-3-Hydroxytetrahydrofuran-4-yl 2,6-Di-*O*-benzyl-α-D-glucopyranoside 3,4,3′-Bis(dibenzyl phosphate) (50). Compound **50** (1.13 g, 74% as an oil) was obtained from **47** (1.22 g, 1.99 mmol) as described above for the synthesis of **48**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.02 (m, 40 H), 5.06 (d, 1 H, J = 3.6 Hz), 5.06−4.34 (m, 19 H), 4.11−4.06 (m, 1 H), 3.97−3.84 (m, 3 H), 3.84−3.66 (m, 4 H), 3.56 (dd, 1 H, J = 3.6, 9.8 Hz); ^{31}P NMR (125 MHz, $CDCl_3$) δ −0.71, −1.58, −1.86; HRMS (FAB) calcd for $C_{66}H_{70}O_{17}P_3$ 1227.3826 $(M + 1)^+$, found 1227.3800.

[(2*R*,3*R*,4*S*)-2-(Benzyloxymethyl)-3-hydroxytetrahydrofuran-4-yl 2,6-Di-*O*-benzyl-α-D-glucopyranoside 3,4,3′-Tris(dibenzyl phosphate) (53). Compound **53** (88 mg, 23% as an oil) was obtained from **52** (200 mg, 0.289 mmol) as described above for the synthesis of **48**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.10 (m, 45 H), 5.12−4.69 (m, 14 H), 4.67 and 4.41 (each d, each 1 H, J = 12.1 Hz), 4.47 and 4.44 (each d, each 1 H, J = 12.3 Hz), 4.43 and 4.31 (each d, each 1 H, J = 11.9 Hz), 4.34−4.17 (m, 3 H), 3.89 (dd, 1 H, J = 5.1, 9.4 Hz), 3.82 (dd, 1 H, J = 3.2, 11.2 Hz), 3.77−3.70 (m, 2 H), 3.66−3.43 (m, 5 H); ^{31}P NMR (125 MHz, $CDCl_3$) δ −0.86, −1.53, −1.81; HRMS (FAB) calcd for $C_{74}H_{78}O_{18}P_3$ 1347.4401 $(M + 1)^+$, found 1347.4330.

(2*R*,3*R*,4*S*)-4-Hydroxy-2-(hydroxymethyl)tetrahydrofuran-3-yl α-D-Glucopyranoside 3,4,4′-Trisphosphate Hexasodium Salt (5). A mixture of **48** (686 mg, 0.510 mmol) and Pd−C (10%, 170 mg) in EtOH (35 mL) was stirred under atmospheric pressure of H_2 at room temperature for 24 h. The catalyst was filtered off with Celite, and the filtrate was evaporated under reduced pressure. The residue was dissolved in H_2O (3 mL) and applied to a Diaion WK-20 resin column (Na^+ form), which was developed by H_2O. The eluent was evaporated under reduced pressure to give **5** (341 mg, quant as a solid) as a sodium salt: ^{1}H NMR (500 MHz, D_2O) δ 5.28 (d, 1 H, J = 3.3 Hz), 4.80−4.70 (m, 1 H), 4.46−4.39 (m, 1 H), 4.29−4.25 (m, 1 H), 4.15−4.08 (m, 2 H), 4.06−3.92 (m, 3 H), 3.84−3.66 (m, 5 H); ^{31}P NMR (125 MHz, D_2O) δ 2.02, 1.66, 0.72; HRMS (FAB) calcd for $C_{11}H_{19}Na_5O_{18}P_3$ 646.9273 $(M + 2H - Na)^+$, found 646.9303.

(2*R*,3*S*,4*S*)-4-Hydroxy-2-(hydroxymethyl)tetrahydrofuran-3-yl α-D-Glucopyranoside 3,4-Bisphosphate Tetrasodium Salt (6). Compound **6** (166 mg, quant as a solid) was obtained as a sodium salt from **49** (360 mg, 0.306 mmol)

as described above for the synthesis of **5**: ^{1}H NMR (500 MHz, D_2O) δ 4.84 (d, 1 H, J = 3.9 Hz), 4.25−4.17 (m, 1 H), 4.12−4.04 (m, 1 H), 3.98 (dd, 1 H, J = 4.7, 7.3 Hz), 3.83−3.70 (m, 4 H), 3.62 (dd, 1 H, J = 2.3, 10.3 Hz), 3.59 (dd, 1 H, J = 2.9, 12.5 Hz), 3.55−3.48 (m, 2 H), 3.48−3.40 (m, 2 H); ^{31}P NMR (125 MHz, D_2O) δ 3.91, 3.66; HRMS (FAB) calcd for $C_{11}H_{19}Na_4O_{15}P_2$ 544.9790 $(M + H)^+$, found 544.9805.

(2*R*,3*R*,4*S*)-3-Hydroxy-2-(hydroxymethyl)tetrahydrofuran-4-yl α-D-Glucopyranoside 3,4,3′-Trisphosphate Hexasodium Salt (7). Compound **7** (34 mg, 91% as a solid) was obtained as a sodium salt from **53** (75 mg, 0.056 mmol) as described above for the synthesis of **5**: ^{1}H NMR (500 MHz, D_2O) δ 5.00 (d, 1 H, H-1, J = 3.9 Hz), 4.48−4.32 (m, 3 H), 4.06−3.85 (m, 5 H), 3.82−3.72 (m, 3 H), 3.66−3.57 (m, 2 H); ^{31}P NMR (125 MHz, D_2O) δ 2.55, 1.98, 1.04; HRMS (FAB) calcd for $C_{11}H_{19}Na_5O_{18}P_3$ 646.9273 $(M + 2H - Na)^+$, found 646.9243.

(3*S*,4*R*)-3-Hydroxytetrahydrofuran-4-yl α-D-Glucopyranoside 3,4,3′-Trisphosphate Hexasodium Salt (8). Compound **8** (40 mg, 89% as a solid) was obtained as a sodium salt from **50** (86 mg, 0.070 mmol) as described above for the synthesis of **5**: ^{1}H NMR (500 MHz, D_2O) δ 5.19 (d, 1 H, J = 3.7 Hz), 4.75−4.67 (m, 1 H), 4.41−4.31 (m, 2 H), 4.00−3.89 (m, 4 H), 3.87−3.78 (m, 3 H), 3.72−3.61 (m, 2 H); ^{31}P NMR (125 MHz, D_2O) δ 2.42, 1.72, 1.15; HRMS (FAB) calcd for $C_{10}H_{16}Na_6O_{17}P_3$ 638.8987 $(M + H)^+$, found 638.8979.

IP_3 Receptor Binding Assay. [^{3}H]IP_3 binding assay was performed as described previously. The compounds were incubated with porcine cerebella homogenate in Tris−HCl buffer (50 mM, pH 8.0, 500 μL) containing EDTA (1 mM) and [^{3}H]IP_3 (2.5 nM) at 4 °C. After 5 min, the samples were centrifuged for 5 min at 4 °C. The supernatant was removed, and the radioactivity in the pellet was then determined. Nonspecific binding was measured in the presence of 1 mM of cold IP_3.

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Supporting Information Available: Copies of the ^{1}H NMR spectra of all new compounds not accompanied by elemental analyses (30 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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