Synthesis of Adenophostin A Analogues Conjugating an Aromatic Group at the 5′-Position as Potent IP_3 Receptor Ligands[1]

Tetsuya Mochizuki,[†] Yoshihiko Kondo,[†] Hiroshi Abe,[†] Stephen C. Tovey,[‡] Skarlatos G. Dedos,[‡] Colin W. Taylor,[‡] Michael Paul,[§] Barry V. L. Potter,[§] Akira Matsuda,[†] and Satoshi Shuto*[,†]

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

Received March 17, 2006

Previous structure−activity relationship studies of adenophostin A, a potent IP_3 receptor agonist, led us to design the novel adenophostin A analogues **5a**−**c**, conjugating an aromatic group at the 5′-position to develop useful IP_3 receptor ligands. The common key intermediate, a D-ribosyl α-D-glucoside **10**α, was stereoselectively synthesized by a glycosidation with the 1-sulfinylglucoside donor **11**, which was conformationally restricted by a 3,4-*O*-cyclic diketal protecting group. After introduction of an aromatic group at the 5-position of the ribose moiety, an adenine base was stereoselectively introduced at the anomeric *β*-position to form **7a**−**c**, where the tetra-*O*-*i*-butyryl donors **9a**−**c** were significantly more effective than the corresponding *O*-acetyl donor. Thus, the target compounds **5a**−**c** were synthesized via phosphorylation of the 2′, 3″, and 4″-hydroxyls. The potencies of compounds **5a**−**c** for Ca^{2+} release were shown to be indistinguishable from that of adenophostin A, indicating that bulky substitutions at the 5′-position of adenophostin A are well-tolerated in the receptor binding. This biological activity of **5a**−**c** can be rationalized by molecular modeling using the ligand binding domain of the IP_3 receptor.

Introduction

Attention has been focused on D-*myo*-inositol 1,4,5-trisphosphate (IP_3, **1**), an intracellular Ca^{2+}-mobilizing second messenger, because of its biological importance.[2] Therefore, analogues of IP_3 have been designed and extensively synthesized to develop specific ligands for IP_3 receptors, which have proven useful in investigating the mechanism of IP_3-mediated Ca^{2+} signaling pathways.[2,3] However, no simple and monomeric analogue has surpassed IP_3 itself either in binding affinity for the IP_3 receptor or in Ca^{2+}-mobilizing activity.[2,3a] In recent studies, however, dimeric analogues of IP_3 have proven to be super-potent in releasing Ca^{2+} from intracellular stores of permeabilized hepatocytes.[3b,c] For example, a short urea-linked dimer of IP_3 of length ∼0.8 nm has an EC_{50} value more than 12-fold lower than IP_3.[3c]

In 1993, Takahashi and co-workers isolated adenophostin A (**2**) from *Penicillium brevicompactum*. They found it to be a very potent IP_3 receptor ligand, 10−100 times more potent than IP_3 in stimulating Ca^{2+} release and binding, with likewise greater affinity than IP_3 to IP_3 receptors.[4] The intriguing structural and biological features have prompted several groups including ours to perform synthetic studies aimed at the design of novel IP_3 receptor ligands.[5−7] Biological evaluation of these analogues, based on adenophostin A, showed that the α-D-glucopyranose structure, the three phosphate groups, and the adenine or another aromatic ring are essential for significant activity.[5] These findings promoted further synthetic studies of adenophostin A analogues, with the aim of developing useful biological tools and/or potential drug leads.

We previously synthesized an adenophostin A analogue **3** lacking the adenine moiety and its des-hydroxymethyl derivative **4** and demonstrated that both compounds bind to IP_3 receptors and stimulate Ca^{2+} mobilization with potencies comparable to IP_3 itself.[5,6a,b] These results suggest that the pentofuranosyl structure of the D-ribose would not be essential for the activity but that the tetrahydrofuran ring could effectively restrict three-dimensional positioning of the D-glucose 3,4-bisphosphate, adenine (aromatic ring), and the third phosphate moiety of the ring. Accordingly, the 5′-hydroxymethyl moiety of adenophostin A seems to be unimportant for the binding and Ca^{2+} mobilization, suggesting that this moiety may be appropriate for further modification to develop novel adenophostin analogues of biological importance.

Bioactive ligands conjugated with an aromatic group, such as a fluorescent or a photoreactive aromatic residue, are useful in labeling target biomolecules and can often effectively clarify the biological mechanism of action. Nagano and co-workers recently developed an IP_3 analogue conjugating malachite green, an aromatic fluorescent residue, at the 1-phosphate moiety to show that the analogue induced specific inactivation of the IP_3 receptors in cells upon laser irradiation.[8] However, the conjugation also reduced its affinity for IP_3 receptors,[8b] suggesting that the 1-phosphate moiety might not be as suitable a site for this kind of conjugating modification. Therefore, identification of another site for the modification of IP_3 receptor ligands without reducing the binding affinity is needed. Adenophostin A might be more suitable as the lead for this kind of modification because of its higher affinity for the receptor compared with IP_3 itself.

Hydrophobic interactions have been recognized to play a crucial role in the binding of many ligands to their target biomolecules.[9] Thus, introduction of an aromatic group to lead compounds sometimes improves binding affinity due to interactions between the aromatic ring and the aromatic and/or aliphatic hydrophobic residues of the target protein located near the binding site. Furthermore, such derivatization sometimes realizes functional inversion of an agonist into an antagonist, which is well-known, for example, in the development of histaminergic[10a]

* To whom correspondence should be addressed. Phone and Fax: +81-11-706-3769. E-mail: shu@pharm.hokudai.ac.jp.
† Hokkaido University.
‡ University of Cambridge.
§ University of Bath.

10.1021/jm060310d CCC: $33.50
Published on Web 08/19/2006

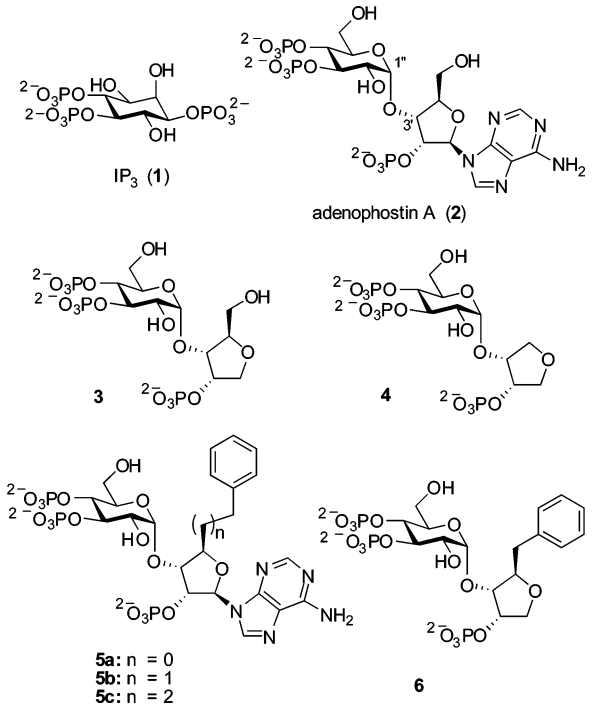


Figure 1. IP_3 (**1**) and adenophostin A (**2**) and its analogues (**3**−**4**).

and adrenergic[10b] receptor antagonists. From this viewpoint, introduction of an aromatic group into an appropriate position of adenophostin A may be interesting.

With these findings in mind, we designed the novel adenophostin A analogues **5a**−**c**[11] having an aromatic group at the 5′-position. In these target compounds, the structures of which are shown in Figure 1, the 5′-hydroxyl in adenophostin A is replaced with a phenyl, benzyl, or phenethyl group. A biological evaluation of these compounds would clarify the steric tolerability around the 5′-hydroxymethyl moiety for introducing a considerably bulky aromatic group in the binding site of the IP_3 receptors. Des-adenine analogue **6**, having a phenyl group at the 5-position, was also designed to confirm the role of the adenine for the receptor binding in this series of the 5′-modified adenophostin A analogues.

Results and Discussion

Synthetic Plan. Our synthetic plan for the target compounds **5a**−**c** and **6** is summarized in Scheme 1. Compounds **7a**−**c**, the effective precursors for the target compounds **5a**−**c**, would be prepared from the disaccharides **8a**−**c** or **9a**−**c** bearing an aromatic residue at the 5-position of the ribose moiety via the β-selective adenine base introduction by the Vorbrüggen glycosylation.[12] Compounds **8a**−**c** and **9a**−**c** could be obtained, via introduction of an aromatic residue at the 5-position of the ribose moiety, from **10**α, which was planned to be synthesized by α-selective glycosidation with the sulfoxide donor **11** and the acceptor **12**. The donor **11** and the acceptor **12** would be prepared from D-glucose and D-xylose, respectively. Sulfoxide glycosyl donors, reported by Kahne and co-workers,[13] are known to be quite stable but are effectively activated under mild Lewis acidic conditions.[13,14] We most recently developed highly α-selective radical and also S_N1 *C*-glycosidation reactions based on the conformational restriction of the pyranosyl donor to the unusual $^4C_1$-form[15] by the 3,4-*O*-cyclic diketal protection.[16] In this restricted conformation, the kinetic anomeric effect was enhanced, resulting in the high α-selectivity in these *C*-glycosidation reactions.[15] On the basis of these results, we designed the sulfoxide donor **11** bearing a 3,4-*O*-cyclic diketal protecting group in this study to realize the desired α-selective glycosidation. The 3,4-*O*-cyclic diketal protecting group also was advantageous for selective phosphorylation of the hydroxyls at a latter stage.[7c]

The α-Selective Glycosidation. The glycosyl donor **11** with the 3,4-*O*-cyclic diketal protection was prepared as reported recently.[11] Glycosidation with the acceptor **12**, prepared according to the previously reported method,[17] and the donor **11** was investigated, and the results are summarized in Table 1. The reactions were carried out under the conditions with Tf_2O and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) as the promoter using CH_2Cl_2, toluene, or Et_2O as the solvent at low temperature.[14] Although the reaction with CH_2Cl_2 as the solvent gave nonstereoselectively a mixture of α/β-glucosidation products (entry 1), the desired α-glucoside **10**α was selectively obtained in the reaction with toluene (entry 2, 50%, $\alpha/\beta = 10:1$) or Et_2O (entry 3, 71%, $\alpha/\beta = 5:1$) as the solvent. We found that the α-glucoside **10**α was obtained as the sole glycosidation product in good yield when the reaction temperature was kept at −78 °C and using Et_2O as the solvent (entry 4).

Synthesis of 5′-Deoxy-5′-phenyladenophostin A. The synthesis of the target compound **5a**, conjugating a phenyl group at the 5′-position, from the α-glucoside **10**α was investigated, as shown in Scheme 2. After removal of the 5-*O*-TBS group of **10**α, oxidation of the 5-hydroxymethyl moiety of the resulting **13** was examined by various methods, where the Moffatt oxidation gave the best result. The resulting aldehyde, without purification because of its instability, was immediately treated with PhMgBr in THF to give the 5-phenyl product **14a** in 52% yield from **13**. Radical deoxygenation at the 5-position was performed by successive treatment of **14a** with PhOCSCl/DMAP in MeCN and with Bu_3SnH/AIBN in heating benzene to form **15a**. Acidic removal of the ketal protecting groups of **15a** followed by acylation produced the 1,2,3′,4′-tetra-*O*-acetate **8a** or the 1,2,3′,4′-tetra-*O*-*i*-butyrylate **9a**.

The Vorbrüggen glycosylation with the acetate **8a** was examined as summarized in Table 2. The reaction was first carried out with N^6-benzoyladenine and TMSOTf/Et_3N in MeCN or dichloroethane (entries 1 and 2), where silylated N^6-benzoyladenine should be formed under the reaction conditions. Although these reactions selectively produced the expected β-nucleoside, the yields were low. The reaction using silylated N^6-benzoyladenine, prepared from N^6-benzoyladenine and hexamethyldisilazane/pyridine, as the acceptor and $SnCl_4$ as the promoter in MeCN improved the yield but was shown to produce the α/β-mixture nonstereoselectively (entry 3).[18]

In the course of the large scale synthetic study of the antitumor nucleoside, 3′-ethynyluridine, we found that an *O*-*i*-butyrylated 3-ethynylribosyl donor was very effective in the Vorbrüggen glycosylation reaction.[19] In the glycosylation with the donors **8a** and **9a**, the steric hindrance due to the 5-phenyl group might disturb the access of the nucleobase to the anomeric β-position, as in the case of the 3′-ethynyluridine synthesis.[19] Therefore, we investigated reactions using the tetra-*O*-*i*-butyryl donor **9a**. Although the reaction using the **9a** by the TMSOTf method was unsuccessful (Table 2, entry 4), the desired β-nucleoside **7a** was selectively obtained in 60% yield when **9a** and silylated N^6-benzoyladenine were treated with $SnCl_4$ at room temperature in MeCN (entry 5). The regio- and stereochemistry of **7a** was confirmed by its NOE and HMBC spectra, as shown in Figure 2.

The three *O*-*i*-butyryl groups of **7a** were removed simultaneously with NaOMe/MeOH to give **16a**. The phosphate units

Scheme 1

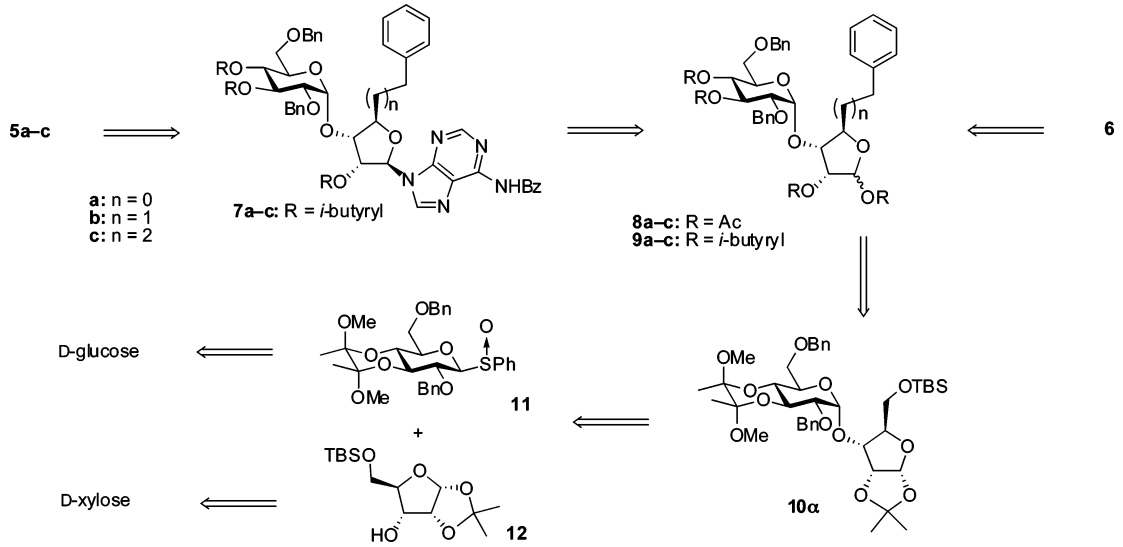


Table 1. Glycosidation with the Donor **11** and the Acceptor **12**[a]

	11 + **12** → **10**α + **10**β				
entry	solvent	temp (°C)	time (h)	yield (%)	α/β[b]
1	CH_2Cl_2	−78 to −40	2	73	1:1
2	toluene	−78 to −20	2	50	10:1
3	Et_2O	−78 to −20	2	71	5:1
4	Et_2O	−78	8	78	only α

[a] Reactions were carried out in Tf_2O (2 equiv) and DTBMP (5 equiv) in the presence of molecular sieves (4A). [b] Determined by ^1H NMR.

were selectively introduced onto the three hydroxyls using the phosphoramidite method with *o*-xylene *N*,*N*-diethylphosphoramidite (XEPA).[20] Thus, **16a** was treated with XEPA and imidazolium triflate[21] in CH_2Cl_2, followed by oxidation with *m*-CPBA, to give the desired 2′,3″,4″-trisphosphate derivative **17a** in 90% yield. Finally, the benzyl protecting groups were all removed in one step by catalytic hydrogenation with Pd black in aqueous MeOH/$CHCl_3$ to furnish the target trisphosphate **5a** in 99% yield as a sodium salt, after treatment with ion-exchange resin.

Synthesis of the Benzyl and Phenethyl Derivatives. The other target compounds, the 5′-benzyl derivative **5b** and the 5′-phenethyl derivative **5c**, were synthesized basically according to the route described above for the synthesis of **5a** (Scheme 2).

Grignard addition of $PhCH_2CH_2MgCl$ to the aldehyde prepared by the Moffatt oxidation of **13** and subsequent Barton deoxygenation gave the 5-phenethyl product **15c**, as in the above case of the 5-phenyl derivative **15a**. On the other hand, in a similar procedure using BnMgCl, the yields of the Grignard addition product and the subsequent deoxygenation product were insufficient (40 and 18%, respectively, Scheme 2).

Compound **13** was converted into the corresponding 5-iodo and 5-*O*-Tf derivatives **18** and **19**, respectively, and their S_N2-type substitution using the benzyl organo-copper reagent was examined (Scheme 3). Treatment of the 5-iodide **18** with BnMgCl/CuI/HMPA in THF[22] produced a mixture of the desired 5-benzyl product **15b** and the 5-chloro product **20** in 77% yield in a ratio of approximately 1:1. However, when the 5-*O*-triflate **19** was subjected to the same reaction conditions, the 5-benzyl product **15b** was isolated in good yield (66%) along with 20% of **20**.

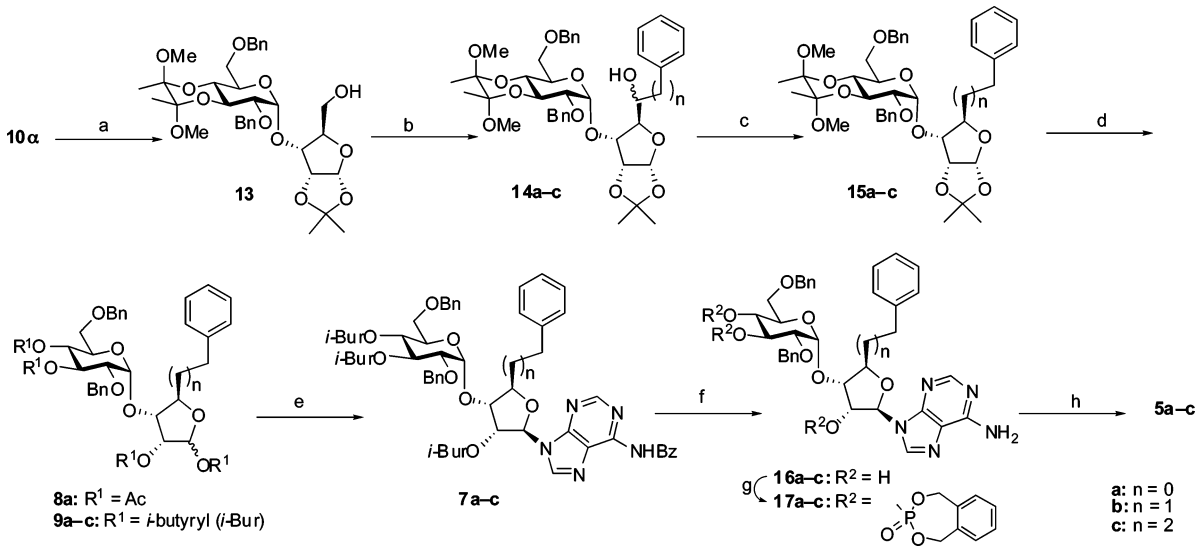
The 5-benzyl and 5-phenethyl products **15b** and **15c** were successfully converted into the target compounds **5b** and **5c**, respectively, via the Vorbrüggen glycosylation and subsequent phosphorylation, as summarized in Scheme 2.

Synthesis of the 5-Phenyl Derivative Lacking the Adenine. The 5-phenyl adenophostin A analogue **6** lacking the adenine moiety was synthesized via hydride reduction at the anomeric position of the furanose moiety of the tetra-*O*-acetyl-5-phenyl derivative **8a** (Scheme 4). When **8a** was treated with Et_3SiH and TMSOTf in CH_2Cl_2 at 0 °C,[23] the expected reduction proceeded effectively and the 2-*O*-acetyl group was concomitantly removed under these conditions to give 60% of the diacetate **22** along with 8% of the corresponding triacetate **21**. After removal of the other acetyl groups of **22** with NaOMe/MeOH, the resulting triol **23** was then phosphorylated and debenzylated by the method described above to produce the final target compound **6**.

Biological Activity. A low affinity Ca^{2+} indicator trapped within the intracellular stores of permeabilized cells was used to monitor Ca^{2+} release mediated by recombinant rat type 1 IP_3 receptors in DT40 cells lacking endogenous IP_3 receptors.[24] Table 3 summarizes the results obtained with each of the compounds, and Figure 3 compares the concentration-dependent Ca^{2+} release by **5b**, as a typical example of the newly synthesized compounds, with those of IP_3 and adenophostin A. Maximally effective concentrations of each of the ligands (IP_3, adenophostin A, **5a**−**c**, and **6**) released a similar fraction of the intracellular Ca^{2+} stores (∼80%), but they differed significantly in their potencies. All the 5′-modified adenophostin analogues **5a**−**c** showed significant Ca^{2+} release similar to the parent compound adenophostin A. The half-maximally effective concentrations (EC_{50}) for **5a** (2.1 ± 0.4 nM), **5b** (2.8 ± 0.6 nM), **5c** (2.7 ± 0.4 nM), and also for adenophostin A (2.1 ± 0.2 nM) are about 13-fold lower than the EC_{50} for IP_3 (24.8 ± 2.1 nM). Compound **6**, the des-adenine analogue of **5a**, had an EC_{50} ∼2-fold higher than that of IP_3

Therefore, **5a**−**c** are full agonists with significant Ca^{2+}-mobilizing potency comparable to adenophostin A. It is interesting that all the three 5′-modified analogues **5a**−**c** have very similar activities, despite their difference in 5′-chain length (*n* = 0, 1, or 2) and closely resemble the parent compound. Thus, the 5′-aromatic moiety of **5a**−**c** does not disturb receptor binding and probably does not interact with the receptor, suggesting that it may be located outside the binding pocket. The dramatic decrease of the Ca^{2+}-mobilizing activity in **6**, the analogue without an adenine, shows that the adenine ring enhances the

Scheme 2



Conditions: (a) TBAF, THF, rt, 82%; (b) (1) Moffatt ox, (2) Grignard reagent, THF, rt, 52% (PhMgBr, **14a**), 40% (BnMgCl, **14b**), 58% ($PhCH_2CH_2MgCl$, **14c**); (c) (1) PhOCSCl, DMAP, MeCN, rt, (2) Bu_3SnH, AIBN, PhH, reflux, 93% (**15a**), 18% (**15b**), 64% (**15c**); (d) (1) 90% TFA, rt, (2) $R^1{}_2O$, Et_3N, DMAP, MeCN, rt, 66% (**8a**), 88% (**9a**), 69% (**9b**), 62% (**9c**); (e) silylated N^6-benzoyladenine, $SnCl_4$, MeCN, rt, 60% (**7a**), 67% (**7b**), 60% (**7c**); (f) NaOMe, MeOH, rt, quant (**16a**), 96% (**16b**), quant (**16c**); (g) XEPA, imidazolium triflate, CH_2Cl_2, −40 °C−rt, then *m*-CPBA, −40 C, 90% (**17a**), 70% (**17b**), quant (**17c**); (h) H_2 (60 psi), Pd-black, aq MeOH−$CHCl_3$, rt, 99% (**5a**), quant (**5b**), 43% (**5c**).

Table 2. Vorbrüggen Glycosylation with Donors **8a** and **9a**

entry	donor	Lewis acid	method[a]	solvent	yield[b] (α/β)
1	**8a**	TMSOTf	A	MeCN	18% (only β)
2	**8a**	TMSOTf	A	$(ClH_2C)_2$	26% (only β)
3	**8a**	$SnCl_4$	B	MeCN	66% (1:1)
4	**9a**	TMSOTf	A	MeCN	12% (only β)
5	**9a**	$SnCl_4$	B	MeCN	60% (only β)

[a] A: N^6-Bz-adenine (4 equiv), TMSOTf (10 equiv), and Et_3N (4 equiv) at room temperature. B: silylated N^6-Bz-adenine (5 equiv), prepared by heating N^6-Bz-adenine in hexamethyldisilazane/pyridine, and $SnCl_4$ (6 equiv) at room temperature. [b] The ratio was determined by ^1H NMR.

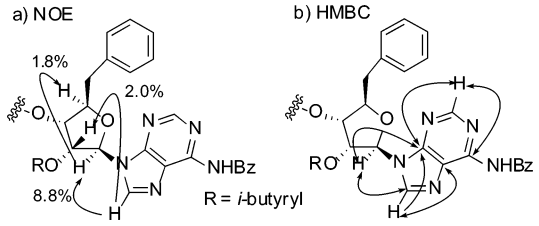
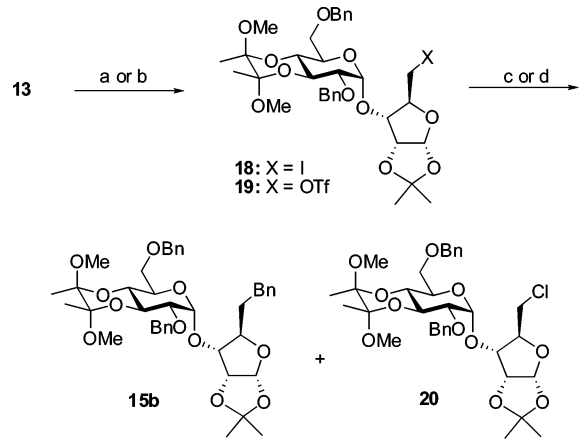


Figure 2. NOE (a) and HMBC (b) data of **7a**.

Scheme 3



Conditions: (a) I_2, Ph_3P, imidazole, PhMe, reflux, 93% (**18**); (b) Tf_2O, DTBMP, CH_2Cl_2, 90% (**19**); (c) **18**, BnMgCl, CuI, HMPA, THF, −50−0 °C, 77% (**15b**/**20** = 1:1); (d) **19**, BnMgCl, CuI, HMPA, THF, −50 °C, 66% (**15b**), 20% (**20**).

activity for a 5′-phenyl derivative, which is consistent with previous results.[6,7]

Conformational Analysis and Molecular Modeling. The conformation of the 5′-deoxy-5′-phenyladenophostin A (**5a**) was investigated by ^1H NMR experiments. The large coupling constants (about 9 Hz) between the protons H-2″, -3″, -4″, and -5″ of the glucose moiety show that the pyranose ring adopts a normal $^4C_1$-chair conformation with the vicinal equatorial *trans*-phosphates, similar to adenophostin A. The coupling constants of the ribose moiety, determined by the proton-decoupling method, were $J_{1',2'} = 3.1$ Hz, $J_{2',3'} = 5.6$ Hz, and $J_{3',4'} = 6.3$ Hz, respectively. The furanose ring of nucleosides generally is in equilibrium between C2′-*endo* and C3′-*endo* forms, and their ratio is known to be calculated by the equation, [C2′-*endo*] (%) $= [J_{1',2'}/(J_{1',2'} + J_{3',4'})] \times 100$.[7e,25] Thus, the [C2′-*endo*] (%) of **5a** was calculated to be 31%, which suggests that the C3′-*endo* form is somewhat more stable than the C2′-*endo* one. However, the energy difference would be rather small, therefore, both of the two forms of **5a** might exist in solution.[26] In NOE experiments of **5a**, when the H-8 of the adenine ring was irradiated, NOEs were observed both at H-1′ (2.9%) and at H-2′ (3.6%) of the ribose moiety, suggesting its *syn*-like conformation around the ribosyl linkage, similar to adenophostin A.

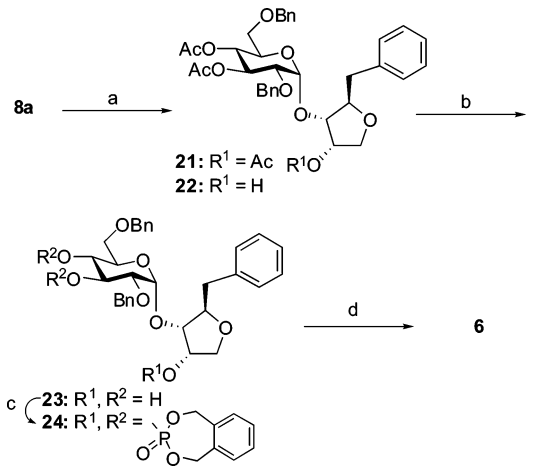
The binding mode of **5a**−**c** to the IP_3 receptor was investigated by molecular modeling using the recently reported X-ray crystal structure of the type 1 IP_3 receptor binding core (1N4K).[27] The structures of the 5′-modified analogues **5a**−**c** were built in MOE (Molecular Operating Environment, v2003.02, Chemical Computing Group, Canada) and minimized using the MMFF94 force field. These structures were then placed in the IP_3 receptor (1N4K) by aligning the 3,4-*trans*-bisphosphate group on the glucose ring with the 4,5-*trans*-bisphosphate of IP_3 from the crystal structure. Following removal of IP_3 from the pocket, the heavy atoms of the receptor and associated water molecules were fixed, and the structure was allowed to minimize. The result is shown in Figure 4, where the side chains are colored magenta (**5a**), green (**5b**), or orange (**5c**). The conformations show that none of the substituents at the

Table 3. Ca^{2+} Release via Type 1 IP_3 Receptors Stimulated by IP_3 and Adenophostin A and Its Analogues

compound	EC_{50}, nM	Hill slope	Ca^{2+} release, %	*n*	relative potency[a]	
					IP_3	adenophostin
IP_3 (**1**)	24.8 ± 2.1	1.21 ± 0.06	78 ± 2	11	1	0.09 ± 0.01
adenophostin A (**2**)	2.1 ± 0.2	1.54 ± 0.13	76 ± 1	12	12.8 ± 4.5	1
5a	2.1 ± 0.4	1.62 ± 0.24	77 ± 1	5	13.4 ± 1.7	1.0 ± 0.23
5b	2.8 ± 0.6	1.16 ± 0.08	76 ± 2	5	12.7 ± 3.8	0.87 ± 0.20
5c	2.7 ± 0.4	1.42 ± 0.16	79 ± 2	6	9.1 ± 1.4	0.87 ± 0.15
6	53.3 ± 10.6	1.11 ± 0.09	79 ± 3	4	0.45 ± 0.05	0.03 ± 0.01

[a] Ca^{2+} release evoked by each of the ligands is shown with potencies relative to IP_3 or adenophostin A, calculated by a comparison of EC_{50} values determined in parallel experiments.

Scheme 4



Conditions: (a) Et_3SiH, TMSOTf, CH_2Cl_2, 0 °C−rt, 8% (**21**), 60% (**22**); (b) NaOMe, MeOH, rt, 86%; (c) XEPA, imidazolium triflate, CH_2Cl_2, −40 °C−rt, then *m*-CPBA, −40 °C, 85%; (d) H_2 (60 psi), Pd-black, aq MeOH−$CHCl_3$, rt, 87%.

5′-position appear to show any favorable interactions with the binding pocket of the receptor as they protrude into areas that probably contain solvent. However, the limitations of this study should be stressed because 1N4K.pdb represents only a truncated form (residues 224−604) of the full length (2700) receptor representing the core binding domain, and it is not known whether the region in question could potentially be accessed by other motifs of the full-length protein with which potential ligand interactions may be possible. Regarding the conformation of the analogues modeled on the receptor, while the preference of a C2′-*endo* conformation in adenophostin A has been previously reported, **5a** seems to prefer a C3′-*endo* solution conformation by NMR, as seen above. In a recent model proposed by some of us for the binding of adenophostin A to its receptor an extended 2′-*endo* conformation with a potential cation-π interaction between adenine and protein was proposed for optimal interaction in the ligand binding domain.[7a] The energy difference between the two C2′-*endo* and C3′-*endo* forms in solution is assumed to be relatively small, and the very high activity of the analogues **5a**−**c**, which is comparable to that of adenophostin A, as reported here, suggests that **5a**−**c** bind to the receptor in a mode similar to that of adenophostin A. Thus, we can propose a 2′-*endo* conformation on the protein, in line with the established model for the parent ligand.

From these results, it may be conjectured that the 5′-aromatic moiety does indeed exist outside the binding pocket during interaction of these analogues **5a**−**c** with the ligand binding domain of the receptor. Therefore, adenophostin A analogues, which are useful as biological tools for labeling target biomolecules potentially could be developed by attaching a functional aromatic residue, such as a fluorescent or photoactive aromatic

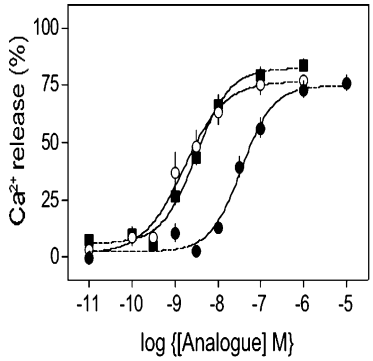


Figure 3. Concentration-dependent release of Ca^{2+} from intracellular stores by IP_3 (●), Adenophostin A (○), and **5b** (■). Results are means ± S.E.M., $n \geq 5$.

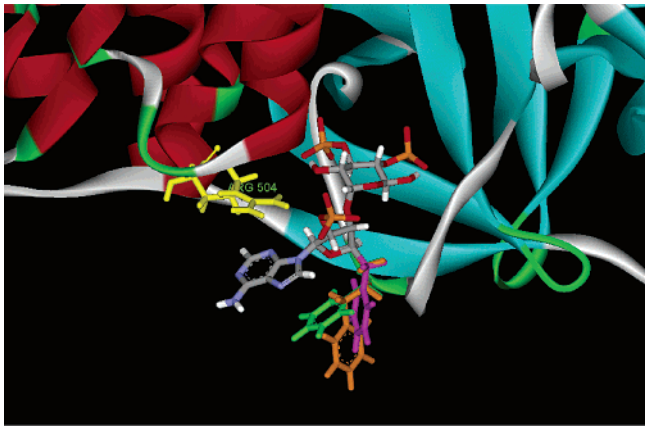


Figure 4. Modeling of analogues **5a**−**c** into the ligand binding domain of the IP_3 receptor. Possible binding modes for **5a** (magenta), **5b** (green), and **5c** (orange) are shown. The adenine moiety of adenophostin A shows a π-stacking interaction with the side-chain of Arg504 as suggested for adenophostin A.[7a]

residue, at the 5′-position. This may become more relevant as the structure of the full length receptor is clarified.

Conclusion. The novel adenophostin A analogues **5a**−**c** conjugating an aromatic group at the 5′-position, designed as novel IP_3 receptor ligands, were synthesized via two key stereoselective glycosidation steps, in which the 1-sulfinylglucoside donor **11** conformationally restricted by a 3,4-*O*-cyclic diketal protecting group and the tetra-*O*-*i*-butyryl donors **9a**−**c**, respectively, were effectively used to realize the desired stereoselectivity. The potencies of **5a**−**c** for the Ca^{2+} mobilization proved to be indistinguishable from that of adenophostin A. This activity can be rationalized by molecular modeling using the ligand binding domain of the IP_3 receptor where, subject to certain caveats, it can be seen that the bulky substitutions have no formal interaction with the protein. We therefore conclude that the 5′-hydroxylmethyl moiety of adenophostin A is not essential for biological activity and that, indeed, this part of

the molecule will tolerate bulky substitutions, which can be effective for conjugating a functional residue.

Experimental Section

General Methods. Chemical shifts are reported in ppm downfield from tetramethylsilane (^{1}H and ^{13}C) or H_3PO_4 (^{31}P), and J values are given in hertz. The ^{1}H NMR assignments described were in agreement with COSY spectra. Thin-layer chromatography was done on Merck coated plates, $60F_{254}$. Silica gel chromatography was carried out using Merck silica gel 7734 or 9385. Reactions were carried out under an argon atmosphere. Compounds **5a**, **11**, and **13** were synthesized as described previously.[11]

General Procedure for the Glycosidation with Donor 11 and Acceptor 12 (Table 1). A mixture of **11** (58 mg, 0.10 mmol), **12** (34 mg, 0.10 mmol), and DTBMP (103 mg, 0.50 mmol) was azeotroped with toluene (3×). To the mixture of the resulting residue and MS4A (powder, 100 mg) in CH_2Cl_2 was slowly added Tf_2O (34 μL, 0.20 mmol) at −78 °C, and the mixture was stirred under the conditions indicated in Table 1. The mixture was poured into aqueous saturated $NaHCO_3$ and filtered through Celite, and the filtrate was partitioned between AcOEt and aqueous saturated $NaHCO_3$. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The resulting residue was purified by flash column chromatography (SiO_2, hexane/AcOEt, 50:1) to give an α/β-mixture of glycosidation products **10**α and **10**β (entries 1−3) or the α-anomer **10**α (entry 4): ^{1}H NMR (α/β-mixture, $CDCl_3$, 270 MHz) for α-anomer δ 7.36−7.20 (m, 10H, Ph × 2), 5.64 (d, 1H, H-1, J = 3.3), 5.16 (d, 1H, H-1′, J = 3.9), 4.79−4.46 (m, 5H, OCH_2Ph × 2, H-2), 4.20−4.04 (m, 3H, H-3, 4, 3′), 3.89−3.54 (m, 7H, H-5a, 5b, 2′, 4′, 5′, 6′a, 6′b), 3.28, 3.15 (each s, each 3H, OCH_3), 1.49, 1.25 (each s, each 3H, Me), 1.31 (s, 6H, isopropylidene), 0.82 (s, 9H, *t*-Bu), 0.013, 0.00 (each s, each 3H, Si−CH_3); for β-anomer δ 7.38−7.17 (m, 10H, Ph × 2), 5.69 (d, 1H, H-1, J = 3.6), 4.80 (m, 2H, OCH_2Ph × 2), 4.67−4.62 (m, 2H, H-2, OCH_2Ph), 4.55 (d, 1H, OCH_2Ph, J = 12.2), 4.46 (d, 1H, H-1′, J = 7.3), 4.06 (m, 1H, H-3), 3.85 (m, 1H, H-4′), 3.80−3.64 (m, 7H, H-4, 5a, 5b, 3′, 5′, 6′a, 6′b), 3.53 (dd, 1H, H-2′, J = 7.3, 8.9), 3.29, 3.17 (each s, each 3H, OCH_3), 1.33, 1.26 (each s, each 3H, Me), 1.32, 1.28 (each s, each 3H, isopropylidene), 0.85 (s, 9H, *t*-Bu), 0.00 (s, 6H, Si−CH_3). **10**α: $[\alpha]^{22.9}_D$ +142.4 (*c* 1.15, $CHCl_3$); FAB-LRMS *m*/*z* 783 (MNa^+). Anal. ($C_{40}H_{60}O_{12}Si$): C, H.

5-Benzyl-5-deoxy-3-*O*-[2,6-di-*O*-benzyl-3,4-*O*-[(2*S*,3*S*)-2,3-dimethoxybutan-2,3-diyl]-α-D-glucopyranosyl]-1,2-*O*-isopropylidene-α-D-ribofuranose (15b) via the Barton Deoxygenation. Compound **14b** (145 mg, 40% as a solid), prepared from **13** (350 mg, 0.54 mmol) by the procedure described for the synthesis of **14a**[11] using BnMgCl (1.0 M in THF) instead of PhMgBr, was used immediately to the next step because of the instability. Thus, treatment of the obtained **14b** (145 mg) by the procedure for the synthesis of **15a**[11] gave **15b** (13 mg, 18% as a solid): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41−7.16 (m, 15H), 5.77 (d, 1H, J = 3.8), 5.22 (d, 1H, J = 3.8), 4.77 (s, 2H), 4.70 (dd, 1H, J = 3.8, 4.3), 4.54, 4.50 (each d, each 1H, J = 12.2), 4.17 (ddd, 1H, H-4, J = 3.6, 3.6, 9.2), 4.14 (dd, 1H, H-3′, J = 9.2, 9.2), 3.84−3.74 (m, 2H), 3.70 (dd, 1H, J = 4.3, 9.2), 3.66−3.32 (m, 3H), 3.28, 3.17 (each s, each 3H), 2.88, 2.72 (each m, each 1H), 2.06, 1.76 (each m, each 1H), 1.52, 1.29 (each s, each 3H), 1.33 (s, 6H); FAB-HRMS calcd for $C_{41}H_{52}O_{11}Na$, 743.3408; found, 743.3431 (MNa^+).

3-*O*-[2,6-Di-*O*-benzyl-3,4-*O*-[(2*S*,3*S*)-2,3-dimethoxybutan-2,3-diyl]-α-D-glucopyranosyl]-1,2-*O*-isopropylidene-5-phenethyl-α-D-ribofuranose (14c). Compound **14c** (118 mg, 58% as a solid) was prepared from **13** (175 mg, 0.27 mmol) by the procedure described for the synthesis of **14a**,[11] using $PhCH_2CH_2MgCl$ (1.0 M in THF) instead of BnMgCl: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52−7.14 (m, 15H), 5.76 (d, 1H, J = 3.8), 5.13 (d, 1H, J = 4.1), 4.80, 4.72 (each d, each 1H, J = 12.2), 4.68 (dd, 1H, J = 3.9, 4.2), 4.56 (m, 2H), 4.19 (dd, 1H, J = 4.2, 9.2), 4.15−4.09 (m, 3H), 3.83 (m, 1H), 3.75−3.58 (m, 4H), 3.30, 3.19 (each s, each 3H), 2.85, 2.69 (each m, each 1H), 2.36 (m, 1H), 2.05−1.82 (m, 2H), 1.59, 1.53 (each s, each 3H), 1.33, 1.28 (each s, each 3H); FAB-LRMS *m*/*z* 773 (MNa). Anal. ($C_{42}H_{54}O_{12}\cdot 1.5H_2O$): C, H.

5-Deoxy-3-*O*-[2,6-di-*O*-benzyl-3,4-*O*-[(2*S*,3*S*)-2,3-dimethoxybutan-2,3-diyl]-α-D-glucopyranosyl]-1,2-*O*-isopropylidene-5-phenethyl-α-D-ribofuranose (15c). Compound **15c** (47 mg, 64%) was prepared from **14c** (75 mg, 0.10 mmol) by the procedure described for the synthesis of **15a**:[11] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42−7.13 (m, 15H), 5.73 (d, 1H, J = 3.8), 5.20 (d, 1H, J = 3.9), 4.79, 4.75 (each d, each 1H, J = 12.4), 4.67 (dd, 1H, J = 3.9, 3.9), 4.54 (s, 2H), 4.16−4.09 (m, 2H), 3.83−3.75 (m, 2H), 3.70−3.60 (m, 4H), 3.30, 3.20 (each s, each 3H), 2.64 (m, 2H), 1.88−1.73 (m, 2H), 1.52, 1.40 (each s, each 3H), 1.25, 0.92 (each m, each 1H), 1.32 (s, 6H); FAB-HRMS calcd for $C_{42}H_{54}O_{11}Na$, 757.3564; found, 757.3560 (MNa^+).

3-*O*-[2,6-Di-*O*-benzyl-3,4-*O*-[(2*S*,3*S*)-2,3-dimethoxybutan-2,3-diyl]-α-D-glucopyranosyl]-5-deoxy-5-iodo-1,2-*O*-isopropylidene-α-D-ribofuranose (18). A mixture of **13** (64 mg, 0.10 mmol), imidazole (27 mg, 0.40 mmol), Ph_3P (52 mg, 0.20 mmol), and I_2 (25 mg, 0.20 mmol) in toluene (2 mL) was heated under reflux for 15 min. After addition of aqueous saturated $NaHCO_3$, I_2 was added to the resulting mixture to turn the aqueous layer brown, and then aqueous saturated $Na_2S_2O_3$ and toluene were added and partitioned. The organic layer was washed with H_2O and brine, dried ($MgSO_4$), and evaporated. The resulting residue was purified by column chromatography (SiO_2, hexane/AcOEt, 9:1) to give **18** (70 mg, 93% as a form): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42−7.23 (m, 10H), 5.79 (d, 1H, J = 3.8), 5.16 (d, 1H, J = 4.1), 4.80 (d, 1H, J = 12.2), 4.76−4.71 (m, 2H), 4.60, 4.54 (each d, each 1H, J = 12.0), 4.11 (dd, 1H, J = 9.9, 9.9), 3.91−3.85 (m, 4H), 3.82 (m, 2H), 3.65 (dd, 1H, J = 4.0, 9.9), 3.57 (dd, 1H, J = 2.8, 11.3), 3.41 (dd, 1H, J = 4.0, 11.3), 3.32, 3.19 (each s, each 3H), 1.55, 1.30 (each s, each 3H,), 1.35 (s, 6H); FAB-HRMS calcd for $C_{34}H_{45}O_{11}INa$ 779.1905, found 779.1894 (MNa^+).

3-*O*-[2,6-Di-*O*-benzyl-3,4-*O*-[(2*S*,3*S*)-2,3-dimethoxybutan-2,3-diyl]-α-D-glucopyranosyl]-5-deoxy-1,2-*O*-isopropylidene-5-*O*-trifluromethanesulfonyl-α-D-ribofuranose (19). To a mixture of **13** (100 mg, 0.15 mmol) and DTBMP (80 mg, 0.38 mmol) in CH_2Cl_2 (1.5 mL) was slowly added a solution of Tf_2O (28 μL, 0.17 mmol) in CH_2Cl_2 (1 mL) at −78 °C, and the mixture was stirred at the same temperature for 1 h. The mixture was partitioned between Et_2O and aqueous saturated $NaHCO_3$, and the organic layer was dried ($MgSO_4$) and evaporated. The resulting residue was purified by column chromatography (SiO_2, hexane/Et_2O, 3:1) to give **19** (105 mg, 90% as a solid): ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.41−7.24 (m, 10H), 5.75 (d, 1H, J = 3.6), 5.08 (d, 1H, J = 4.0), 4.82 (d, 1H, J = 12.2), 4.77−4.63 (m, 4H), 4.57, 4.50 (each d, each 1H, J = 12.2), 4.36 (m, 1H), 4.11 (dd, 1H, J = 9.6, 9.6), 4.00 (dd, 1H, J = 4.2, 9.2), 3.86−3.58 (m, 5H), 3.32, 3.18 (each s, each 3H), 1.54, 1.29 (each s, each 3H), 1.34 (s, 6H); FAB-HRMS calcd for $C_{35}H_{45}F_3O_{14}SNa$, 801.2380; found, 801.2393 (MNa^+). Anal. ($C_{35}H_{45}F_3O_{14}S$): C, H, S.

Compound 15b from 19. After stirring a mixture of CuI (662 mg, 3.47 mmol) and BnMgCl (1.0 M in THF, 7.0 mL, 7.0 mmol) in HMPA (8 mL) and THF (17 mL) at −50 °C for 1 h, a solution of **19** (846 mg, 1.08 mmol) in THF (10 mL) was slowly added. The resulting mixture was stirred at the same temperature for 2 h, and then aqueous saturated NH_4Cl and Et_2O were added. The mixture was partitioned, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The resulting residue was purified by column chromatography (SiO_2, hexane/AcOEt, 10:1) to give **15b** (515 mg, 66%) and **5-chloro-5-deoxy-3-*O*-[2,6-di-*O*-benzyl-3,4-*O*-[(2*S*,3*S*)-2,3-dimethoxbutan-2,3-diyl]-α-D-glucopyranosyl]-1,2-*O*-isopropylidene-α-D-ribofuranose (20):** $[\alpha]^{20.7}_D$ +154.1 (*c* 1.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32−7.23 (m, 10H), 5.79 (d, 1H, J = 3.6), 5.16 (d, 1H, J = 4.1), 4.80, 4.74 (each d, each 1H, J = 12.5), 4.71 (m, 1H), 4.58, 4.52 (each d, each 1H, J = 12.1), 4.42 (ddd, 1H, J = 3.2, 3.2, 11.6), 4.15−4.09 (m, 2H), 3.88 (ddd, 1H, J = 2.0, 12.6, 12.6), 3.84−3.70 (m, 5H), 3.65 (dd, 1H, J = 3.9, 9.9), 3.32, 3.18 (each s, each 3H), 1.55, 1.30 (each s, each 3H), 1.35 (s, 6H); FAB-HRMS calcd for $C_{34}H_{45}ClO_{11}Na$, 687.2548; found, 687.2568 (MNa^+).

5-Benzyl-5-deoxy-3-*O*-(2,6-di-*O*-benzyl-3,4-di-*O*-isobutyryl-α-D-glucopyranosyl)-1,2-di-*O*-isobutyryl-D-ribofuranose (9b). Com-

pound **9b** (40 mg, 69% as a solid) was prepared from **15b** (50 mg, 0.068 mmol) by the procedure described for the synthesis of **9a**:[11] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34−7.12 (m, 15H), 6.47 (d, 0.15H, $J_{1,2} = 4.6$), 6.13 (s, 0.85H), 5.42 (m, 1H), 5.32 (d, 1H, $J = 4.3$), 5.04 (m, 1H), 4.91 (d, 0.85H, $J = 3.6$), 4.74 (d, 0.15H, $J = 3.2$), 4.57−4.40 (m, 4H), 4.30 (m, 1H), 4.21(m, 1H), 3.89 (m, 1H), 3.55 (dd, 1H, $J = 3.4, 9.9$), 3.30 (m, 2H), 2.78, 2.64 (each m, each 1H), 2.55−2.34 (m, 4H), 2.07, 1.81 (each m, each 1H), 1.28−0.97 (m, 24H); FAB-HRMS calcd for $C_{48}H_{62}O_{13}Na$, 869.4088; found, 869.4083 (MNa^+).

5-Deoxy-3-*O*-(2,6-di-*O*-benzyl-3,4-di-*O*-isobutyryl-α-D-glucopyranosyl)-1,2-di-*O*-isobutyryl-5-phenethyl-D-ribofuranose (9c). Compound **9c** (41 mg, 62% as a solid) was prepared from **15c** (57 mg, 0.077 mmol) by the procedure described for the synthesis of **9a**:[11] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34−7.11 (m, 15H), 6.42 (d, 0.2H, $J = 3.6$), 6.02 (s, 0.8H), 5.28 (m, 1H), 5.08 (d, 0.8H, $J = 9.9$), 5.02 (m, 1H), 4.93 (m, 1H), 4.74 (d, 0.20H, $J = 3.3$), 4.57−4.39 (m, 4H), 4.23 (m, 1H), 4.15 (m, 1H), 3.86 (m, 1H), 3.55 (dd, 1H, $J = 3.3, 9.9$), 3.35 (m, 2H), 2.60 (t, 2H, $J = 6.4$), 2.54−2.31 (m, 4H), 1.85−1.46 (m, 4H), 1.13−0.98 (m, 24H); FAB-HRMS calcd for $C_{49}H_{64}O_{13}Na$, 883.4244; found, 883.4274 (MNa^+).

***N*^{6}-Benzoyl-9-[5-benzyl-5-deoxy-3-*O*-(2,6-di-*O*-benzyl-3,4-di-*O*-isobutyryl-α-D-glucopyranosyl)-2-*O*-isobutyryl-β-D-ribofuranosyl]adenine (7b).** Compound **7b** (169 mg, 67% as a solid) was prepared from **9b** (200 mg, 0.24 mmol) by the procedure described for the synthesis of **7a** (Table 2, entry 5):[11] $[\alpha]^{20.7}_D$ +35.5 (*c* 1.58, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.99 (br s, 1H, NH), 8.80 (s, 1H, H-2), 8.10 (s, 1H, H-8), 8.30 (m, 2H, *o*-Bz), 7.61 (m, 3H, *m*-, *p*-Bz), 7.32−7.11 (m, 15H, Ph × 3), 6.19 (d, 1H, H-1′, $J = 6.4$), 5.99 (dd, 1H, H-2′, $J = 5.3, 6.4$), 5.49 (dd, 1H, H-3″, $J = 9.8, 10.2$), 5.09 (dd, 1H, H-4″, $J = 9.8, 9.8$), 4.92 (d, 1H, H-1″, $J = 3.2$), 4.59−4.49 (m, 4H, H-3′, OCH_2Ph × 3), 4.43 (d, 1H, OCH_2-Ph, $J = 11.1$), 4.37 (m, 1H, H-4′), 3.97 (ddd, 1H, H-5″, $J = 2.0, 2.0, 10.2$), 3.58 (dd, 1H, H-2″, $J = 3.6, 10.2$), 3.36 (dd, 1H, H-6″a, $J = 4.5, 10.2$), 3.30 (dd, 1H, H-6″b, $J = 2.0, 10.2$), 2.27, 2.62 (each m, each 1H, H-6′a, 6′b), 2.51−2.37 (m, 3H, COCH(CH_3)$_2$ × 3), 2.19, 2.10 (each m, each 1H, H-5′a, 5′b), 1.26 (t, 3H, COCH(CH_3)$_2$), 1.21−1.00 (m, 15H, COCH(CH_3)$_2$ × 3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.9, 152.6, 149.5, 144.3, 141.3, 139.7, 138.4, 138.4, 131.5, 128.1, 128.1, 128.0, 127.9, 127.2, 127.1, 125.6, 119.1, 110.3, 96.1, 95.3, 87.0, 81.9, 78.9, 77.3, 72.3, 72.1, 71.8, 71.3, 70.3, 69.7, 41.0, 40.1, 39.9, 35.2, 32.4, 31.2, 29.8, 28.4, 23.3, 22.4, 21.2, 18.9, 16.36, 13.9, 11.2, 10.8.

***N*^{6}-Benzoyl-9-[5-deoxy-3-*O*-(2,6-di-*O*-benzyl-3,4-di-*O*-isobutyryl-α-D-glucopyranosyl)-2-*O*-isobutyryl-5-phenethyl-β-D-ribofuranosyl]adenine (7c).** Compound **7c** (30 mg, 60% as a solid) was prepared from **9c** (110 mg, 0.11 mmol) by the procedure described for the synthesis of **7a** (Table 2, entry 5):[11] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.02 (br s, 1H, NH), 8.75 (s, 1H, H-2), 8.06 (s, 1H, H-8), 8.03 (m, 2H, *o*-Bz), 7.53 (m, 3H, *m*-, *p*-Bz), 7.34−7.09 (m, 15H, Ph × 3), 6.14 (d, 1H, H-1′, $J = 5.0$), 5.91 (dd, 1H, H-2′, $J = 5.0, 5.0$), 5.49 (dd, 1H, H-3″, $J = 9.8, 9.8$), 5.09 (dd, 1H, H-4″, $J = 9.8, 9.8$), 4.90 (d, 1H, H-1″, $J = 3.6$), 4.59−4.28 (m, 6H, H-3′, -4′, OCH_2Ph × 4), 3.99 (m, 1H, H-5″), 3.58 (dd, 1H, H-2″, J_2″, 1″ = 3.6, J_2″, 3″ = 9.8), 3.38 (m, 2H, H-6″a, 6″b), 2.59 (t, 2H, H-7′, $J = 7.6$), 2.51−2.41 (m, 3H, COCH(CH_3)$_2$ × 3), 1.82−1.60 (m, 4H, H-5′a,b, 6′a,b), 1.12−1.02 (m, 18H, COCH(CH_3)$_2$ × 3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.0, 175.4, 152.6, 151.3, 149.5, 142.0, 133.5, 132.8, 132.3, 130.8, 128.8, 128.7, 128.40, 128.3, 128.3, 128.0, 127.8, 127.7, 125.8, 123.6, 98.3, 87.8, 83.3, 79.6, 77.6, 73.6, 73.4, 73.2, 71.2, 69.7, 68.5, 67.92, 35.6, 34.1, 33.9, 33.7, 19.1, 18.9, 18.8; FAB-HRMS calcd for $C_{57}H_{66}N_5O_{12}$, 1012.4708; found, 1012.4750 (MH^+).

9-[5-Benzyl-5-deoxy-3-*O*-(2,6-di-*O*-benzyl-α-D-glucopyranosyl)-β-D-*ribo*-pentofuranosyl] adenine (16b). Compound **16b** (72 mg, 96% as a solid) was prepared from **7b** (110 mg, 0.11 mmol) by the procedure described for the synthesis of **16a**:[11] $[\alpha]^{202.3}_D$ +50.1 (*c* 0.57, CH_3OH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.36 (s, 1H), 8.14 (s, 1H), 7.41−7.10 (m, 17H), 5.93 (d, 1H, $J = 6.4$), 5.31 (d, 1H, $J = 3.2$), 5.29 (d, 1H, $J = 5.8$), 5.01 (m, 1H), 4.79, 4.60 (each d, each 1H, $J = 11.4$), 4.49, 4.45 (each d, each 1H, $J = 12.6$), 4.30 (m, 1H), 4.03 (m, 1H), 3.69−3.63 (m, 2H), 3.51 (m, 1H), 3.46−3.29 (m, 2H), 3.25 (dd, 1H, $J = 3.2, 9.8$), 2.57 (m, 2H), 1.98 (m, 2H); UV (MeOH) λ_{max} 261 nm; FAB-HRMS calcd for $C_{37}H_{42}N_5O_8$, 684.3034; found, 684.3044 (MH^+).

9-[5-Deoxy-3-*O*-(2,6-di-*O*-benzyl-α-D-glucopyranosyl)-5-phenethyl-β-D-ribofuranosyl]adenine (16c). Compound **16c** (13 mg, quant. as a solid) was prepared from **7c** (19 mg, 0.019 mmol) by the procedure described for the synthesis of **16a**:[11] ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.31 (s, 1H), 8.12 (s, 1H),7.56−7.07 (m, 17H), 5.89 (d, 1H, $J = 4.4$), 5.28 (m, 1H), 5.23 (br s, 1H), 4.94 (m, 1H), 4.78, 4.61 (each d, each 1H, $J = 11.4$), 4.44 (m, 2H), 4.23 (m, 1H), 4.03 (m, 1H), 3.68−3.64 (m, 2H), 3.52−3.24 (m, 5H), 3.14 (dd, 1H, $J = 8.5, 8.5$), 2.48 (m, 2H), 1.67−1.22 (m, 4H); UV (MeOH) λ_{max} 259 nm; FAB-HRMS calcd for $C_{38}H_{43}N_5O_8$-Na, 720.3009; found, 720.2998 (MNa^+).

5′-Deoxy-5′-benzyladenophostin A Trisphosphate Derivative 17b. Compound **17b** (75 mg, 70% as a solid) was prepared from **16b** (60 mg, 0.088 mmol) by the procedure described for the synthesis of **17a**:[11] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.21 (s, 1H), 7.76 (s, 1H), 7.46−6.98 (m, 29H), 6.17 (d, 1H, $J = 5.8$), 5.96 (m, 1H), 5.67 (s, 2H), 5.41 (m, 2H), 5.32 (d, 1H, $J = 3.6$), 5.19−4.76 (m, 12H), 4.64, 4.52 (each d, each 1H, $J = 12.0$), 4.57 (dd, 1H, $J = 4.0, 4.0$), 4.23 (m, 1H), 3.95 (m, 1H), 3.71−3.67 (m, 2H), 3.64 (dd, 1H, $J = 3.6, 9.8$), 2.72, 2.57 (each m, each 1H), 2.18, 2.02 (each m, each 1H); FAB-HRMS calcd for $C_{61}H_{63}N_5O_{17}P_3$, 1230.3432; found, 1230.3445 (MH^+).

5′-Deoxy-5′-phenethyladenophostin A Trisphosphate Derivative 17c. Compound **17c** (31 mg, quant. as a solid) was prepared from **16c** (17 mg, 0.024 mmol) by the procedure described for the synthesis of **17a**:[11] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (s, 1H), 7.67 (s, 1H), 7.38−6.99 (m, 29H), 6.07 (d, 1H, $J = 5.8$), 5.82 (dd, 1H, $J = 5.8, 12.6$), 5.42−5.27 (m, 2H), 5.23 (d, 1H, $J = 3.6$), 5.11−4.67 (m, 16H), 4.45 (m, 1H), 4.22 (m, 1H), 3.92 (m, 1H), 3.69−3.61 (m, 2H), 3.60 (dd, 1H, $J = 3.6, 9.8$), 2.47 (m, 2H), 1.81−1.51 (m, 4H); FAB-HRMS calcd for $C_{62}H_{65}N_5O_{17}P_3$, 1244.3589; found, 1244.3560 (MH^+).

5′-Deoxy-5′-benzyladenophostin A 2′,3″,4″-Trisphosphate (5b). Compound **5b** (35 mg, quant. as a solid) was prepared from **17b** (54 mg, 0.044 mmol) by the procedure described for the synthesis of **5a**:[11] ^{1}H NMR (D_2O, 400 MHz) δ 8.34 (s, 1H, H-2), 8.31 (s, 1H, H-8), 7.38−7.24 (m, 5H, Ph), 6.31 (m, 1H, H-1′), 5.38 (m, 1H, H-2′), 5.29 (m, 1H, H-1″), 4.67 (m, 1H, H-4′), 4.51 (m, 1H, H-3′), 4.38 (m, 1H, H-3″), 4.09−4.05 (m, 2H, H-4″, H-5″), 3.77 (m, 1H, H-2″), 3.67 (m, 1H, H-6″a), 3.57 (m, 1H, H-6″b), 3.20 (m, 2H, H-6′a,b), 2.71 (m, 2H, H-5′a,b); ^{31}P NMR ($CDCl_3$, 202 MHz, H-decoupled) δ −3.38, −3.60, −3.97; UV (H_2O) λ_{max} 259 nm; FAB-HRMS calcd for $C_{23}H_{31}N_5O_{17}P_3$, 742.0928; found, 742.0905 [(M − H)$^-$].

5′-Deoxy-5′-phenethyladenophostin A 2′,3″,4″-Trisphosphate (5c). Compound **5c** (8 mg, 43% as a solid) was prepared from **20c** (31 mg, 0.025 mmol) by the procedure described for the synthesis of **5a**:[11] ^{1}H NMR (D_2O, 400 MHz) δ 8.34 (s, 1H, H-2), 8.31 (s, 1H, H-8), 7.38−7.24 (m, 5H, Ph), 6.31 (m, 1H, H-1′), 5.38 (m, 1H, H-2′), 5.29 (m, 1H, H-1″), 4.67 (m, 1H, H-4′), 4.51 (m, 1H, H-3′), 4.38 (m, 1H, H-3″), 4.09−4.05 (m, 2H, H-4″, H-5″), 3.77 (m, 1H, H-2″), 3.67 (m, 1H, H-6″a), 3.57 (m, 1H, H-6″b), 3.20 (m, 2H, H-6′a,b), 2.71 (m, 2H, H-5′a,b); ^{31}P NMR (D_2O, 202 MHz, H-decoupled) δ −2.00, −3.29, −3.88; UV (H_2O) λ_{max} 259 nm; FAB-HRMS calcd for $C_{24}H_{33}N_5O_{17}P_3$, 756.1083; found, 756.1084 [(M − H)$^-$].

(2*R*,3*R*,4*S*)-4-Acetoxy-2-benzyl-tetrahydrofuran-3-yl 3,4-di-*O*-acetyl-2,6-di-*O*-benzyl-α-D-glucopyranoside (21) and (2*R*,3*R*,4*S*)-2-Benzyl-4-hydroxytetrahydrofuran-3-yl 3,4-di-*O*-acetyl-2,6-di-*O*-benzyl-α-D-glucopyranoside (22). To a mixture of **8a** (20 mg, 0.028 mmol), Et_3SiH (13 μL, 0.056 mmol) in CH_2Cl_2 (0.5 mL) was slowly added TMSOTf (10 μL, 0.056 mmol) at 0 °C, and the mixture was stirred at the same temperature for 20 min. The mixture was partitioned between $CHCl_3$ and aqueous saturated $NaHCO_3$, and the organic layer was washed with H_2O and brine, dried ($MgSO_4$), and evaporated. The resulting residue was purified by column chromatography (SiO_2, hexane/AcOEt, 5:1−3:1) to give

21 (2 mg, 8% as a foam) and **22** (11 mg, 60% as a foam). **21**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33−7.21 (m, 15H), 5.42 (dd, 1H, J = 9.5, 9.5), 5.25 (m, 1H), 5.03 (dd, 1H, J = 9.5, 9.5), 5.00 (d, 1H, J = 3.2), 4.64, 4.56, 4.49, 4.44 (each d, each 1H, J = 12.1), 4.63 (m, 1H), 4.08 (dd, 1H, J = 5.1, 10.1), 4.00 (dd, 1H, J = 5.3, 6.9), 3.88 (ddd, 1H, J = 3.4, 6.9, 10.1), 3.81 (dd, 1H, J = 3.7, 10.1), 3.56 (dd, 1H, J = 3.6, 10.1), 3.41 (m, 2H), 3.07 (dd, 1H, J = 4.0, 14.1), 2.75 (dd, 1H, J = 8.1, 14.1), 2.00, 1.90, 1.89 (each s, each 3H); FAB-HRMS calcd for $C_{37}H_{43}O_{11}$, 663.2806; found, 663.2831 (MH^+). **22**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36−7.17 (m, 15H), 5.42 (dd, 1H, J = 9.8, 9.8), 5.05 (dd, 1H, J = 9.8, 9.8), 4.80 (d, 1H, J = 3.2), 4.67, 4.58, 4.56, 4.42 (each d, each 1H, J = 12.1), 4.18 (m, 1H), 4.07 (m, 1H), 4.98 (dd, 1H, J = 5.1, 10.1), 3.83−3.80 (m, 2H), 3.69 (dd, 1H, J = 3.7, 10.1), 3.64−3.61 (m, 2H), 3.37 (m, 2H), 3.36 (dd, 1H, J = 4.0, 14.1), 2.85 (dd, 1H, J = 8.1, 14.1), 2.00, 1.90, (each s, each 3H); FAB-HRMS calcd for $C_5H_{41}O_{10}$, 621.2700; found, 621.2710 (MH^+).

(2*R*,3*R*,4*S*)-2-Benzyl-tetrahydrofuran-3-yl 2,6-Di-*O*-benzyl-α-D-glucopyranoside (23). Compound **23** (7 mg, 86% as a solid) was prepared from **22** (10 mg, 11 μmol) by the procedure described for the synthesis of **16a**:[11] ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.38−7.14 (m, 15H), 5.14 (br s, 1H), 5.07 (d, 1H, J = 3.4), 4.73, 4.66 (each d, each 1H, J = 11.7), 4.49, 4.46 (each d, each 1H, J = 12.6), 4.33 (d, 1H), 4.12 (m, 1H), 3.95 (m, 1H), 3.84 (dd, 1H, J = 5.1, 9.3), 3.79 (dd, 1H, J = 5.7, 5.7), 3.64−3.57 (m, 3H), 3.52−3.46 (m, 3H), 3.22 (dd, 1H, J = 3.4, 9.4), 3.14 (dd, 1H, H-4, J = 9.3, 9.3), 2.90 (dd, 1H, J = 3.7, 13.9), 2.63 (dd, 1H, J = 7.9, 13.9); FAB-HRMS calcd for $C_{31}H_{37}O_8$, 537.2487; found, 537.2473 (MH^+).

Trisphosphate Derivative 24. Compound **24** (38 mg, 85% as a solid) was prepared from **23** (22 mg, 0.040 mmol) by the procedure described for the synthesis of **17a**:[11] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42−7.11 (m, 27H), 5.47−5.32 (m, 2H), 5.24−4.74 (m, 15H), 4.66, 4.60, 4.53 (each d, each 1H, J = 11.9), 4.32 (m, 1H), 4.06 (dd, 1H, J = 3.4, 10.5), 4.00 (dd, 1H, J = 4.2, 10.5), 3.93 (m, 1H), 3.82 (m, 1H), 3.76−3.67 (m, 2H), 3.64 (dd, 1H, J = 3.6, 9.8), 3.05 (dd, 1H, J = 10.0, 14.2), 2.76 (dd, 1H, J = 3.5, 14.2); FAB-HRMS calcd for $C_{55}H_{58}O_{17}P_3$, 1083.2887; found, 1083.2880 (MH^+).

(2*R*,3*R*,4*S*)-2-Benzyl-4-hydroxytetrahydrofuran-3-yl 3,4-Di-α-D-glucopyranoside Trisphosphate (6). Compound **6** (15 mg, 87% as a solid) was prepared from **24** (31 mg, 0.029 mmol) by the procedure described for the synthesis of **5a**:[11] ^{1}H NMR (D_2O, 400 MHz) δ 7.30−7.19 (m, 5H, Ph), 5.04 (d, 1H, H-1, J = 3.6), 4.76 (m, 1H, H-4′), 4.31 (m, 1H, H-2′), 4.32 (m, 1H, H-3), 4.07 (dd, 1H, H-3′, J = 5.3, 5.3), 4.01−3.89 (m, 3H, H-4, H-5′a,b), 3.61−3.55 (m, 2H, H-2, H-6a), 3.49 (m, 1H, H-6b), 3.06 (m, 1H, H-5), 2.92 (m, 2H, CH_2Ph); ^{31}P NMR (D_2O, 202 MHz, H-decoupled) δ 0.51, 0.35, 0.02; FAB-HRMS calcd for $C_{17}H_{26}O_{17}P_3$, 595.0377; found, 595.0380 [$(M - H)^-$].

Biological Methods. The effects of compounds on intracellular Ca^{2+} stores of a stable cell line expressing rat type 1 IP_3 receptor (DT40-IP_3R1 cells) were measured using a low-affinity Ca^{2+} indicator trapped within the intracellular stores of permeabilized cells as described previously.[24]

Molecular Modeling. Ligand structures were built in MOE starting from unconstrained cyclopentane. Constraints were added to this ring to ensure that the final structure had the 2′-endo conformation. The structure was built up to give adenophostin A, minimizing at each stage (i.e., adding the glucose, then the phosphates and finally the adenine ring) using the MMFF94 force field. Once the adenophostin A molecule had been built, the 5′-modified analogues were derived by adding substituents at the 5′ position using $(CH_2)_nC_6H_5$, where n = 1, 2, 3. These structures were then placed in the IP_3 receptor (1N4K) by aligning the 3,4-*trans*-bisphosphate on the glucose ring with the 4,5-*trans*-bisphosphate of IP_3 from the crystal structure.[27] Following removal of IP_3 from the structure, the heavy atoms of the receptor and associated water molecules were fixed, and the structure was allowed to minimize.

Acknowledgment. We wish to acknowledge financial support from Ministry of Education, Culture, Sports, Science and Technology, Japan for Scientific Research 17659027 and 17390027 (to S.S.), the Japan Society for Promotion of Science for Creative Scientific Research 13NP0401 (to A.M.), and the Wellcome Trust for Program Grants 039662 (to C.W.T.) and 060554 (to B.V.L.P.).

Supporting Information Available: Purities of compounds by combustion analysis and HPLC (^{1}H NMR charts of **5a**, **5b**, **5c**, and **6**.

References

(1) This report constitutes Part 243 of Nucleosides and Nucleotides: For Part 242: Inoue, N.; Minakawa, N.; Matsuda, A. Synthesis and properties of 4′-thioDNA: unexpected RNA-like behavior of 4′-thioDNA. *Nucleic Acids Res.* **2006**, *34*, 3476−3483.

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

(3) (a) Potter, B. V. L.; Lampe, D. Chemistry of inositol lipid mediated cellular signaling. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1933−1972. (b) Riley, A. M.; Morris, S. A.; Nerou, E. P.; Correa, V.; Potter, B. V. L.; Taylor, C. W. Interactions of inositol 1,4,5-trisphosphate (IP_3) receptors with synthetic poly(ethylene glycol)-linked dimers of IP_3 suggest close spacing of the IP_3-binding sites. *J. Biol. Chem.* **2002**, *277*, 40290−40295. (c) Riley, A. M.; Laude, A. J.; Taylor, C. W.; Potter, B. V. L. Dimers of D-*myo*-inositol 1,4,5-trisphosphate: design, synthesis, and interaction with Ins(1,4,5)P_3 receptors. *Bioconjugate Chem.* **2004**, *15*, 278−289 and references therein.

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

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

(6) (a) Tatani, K.; Shuto, S.; Ueno, Y.; Matsuda, A. Synthesis of 1-*O*-[(3*S*,4*R*)-3-hydroxytetrahydrofuran-4-yl]-α-D-glucopyranoside 3,4,3′-trisphosphate as a novel potent IP_3 receptor ligand. *Tetrahedron Lett.* **1998**, *39*, 5065−5068. (b) Shuto, S.; Tatani, K.; Ueno, Y.; Matsuda, A. Synthesis of adenophostin analogues lacking the adenine moiety as novel potent IP_3 receptor ligands: Some structural requirements for the significant activity of adenophostin A. *J. Org. Chem.* **1998**, *63*, 8815−8824. (c) Kashiwayanagi, M.; Tatani, K.; Shuto, S.; Matsuda, A. Inward current responses to IP_3 and adenophostin-analogues in turtle olfactory sensory neurons. *Eur. J. Neurosci.* **2000**, *12*, 606−612. (d) Abe, H.; Shuto, S.; Matsuda, A. Synthesis of the *C*-glycosidic analogue of adenophostin A, a potent IP_3 receptor agonist, using a temporary silicon-tethered radical coupling reaction as the key step. *Tetrahedron Lett.* **2000**, *41*, 2391−2394. (e) Abe, H.; Shuto, S.; Matsuda, A. Synthesis of the *C*-glycosidic analogue of adenophostin A and its uracil congener as potential IP_3 receptor ligands. Stereoselective construction of the *C*-glycosidic structure by a temporary silicon-tethered radical coupling reaction. *J. Org. Chem.* **2000**, *65*, 4315−4325. (f) Shuto, S.; Yahiro, Y.; Ichikawa, S.; Matsuda, A. Synthesis of 3,7-anhydro-D-*glycero*-D-*ido*-octitol 1,5,6-trisphosphate as an IP_3 receptor ligand using a radical cyclization reaction with a vinylsilyl tether as the key step. Conformational restriction strategy using steric repulsion between adjacent bulky protecting groups on a pyranose ring. *J. Org. Chem.* **2000**, *65*, 5547−5557. (g) Terauchi, M.; Yahiro, T.; Abe, H.; Ichikawa, S.; Tovey, S. C.; Dedos, S. G.; Taylor, C. W.; Potter, B. V. L.; Matsuda, A.; Shuto, S. Synthesis of 4,8-anhydro-D-*glycero*-D-*ido*-nonanitol 1,6,7-trisphosphate as a novel IP_3 receptor ligand using a stereoselective radical cyclization reaction based on a conformational restriction strategy. *Tetrahedron* **2005**, *61*, 3697−3707.

(7) (a) Rosenberg, H. J.; Riley, A. M.; Laude, A. J.; Taylor, C. W.; Potter, B. V. L. Synthesis and Ca^{2+}-mobilizing activity of purine-modified mimics of adenophostin A: a model for the adenophostin-Ins(1,4,5)-P_3 receptor interaction. *J. Med. Chem.* **2003**, *46*, 4860−4871 and

references therein. (b) Wilcox, R. A.; Erneux, C.; Primrose, W. U.; Gigg, R.; Nahorski, S. R. 2-Hydroxyethyl D-glucopyranoside 2,3′,4′-trisphosphate, a novel, metabolically resistant, adenophostin A and *myo*-inositol 1,4,5-trisphosphate analogue potently interacts with the *myo*-inositol 1,4,5-trisphosphate receptor. *Mol. Pharmacol.* **1995**, *47*, 1201−1211. (c) de Kort, M.; Regenbogen, A. D.; Overkleeft, H. S.; Challis, J.; Iwata, Y.; Miyamoto, S.; van der Marel, G. A.; van Boom, J. Synthesis and biological evaluation of cyclophostin: a 5′,6′-tethered analogue of adenophostin A. *Tetrahedron* **2000**, *56*, 5915−5928 and references therein. (d) Roussel, F.; Moitessier, N.; Hilly, M.; Chrétien, F.; Mauger, J.-P.; Chapleur, Y. *Bioorg. Med. Chem.* **2002**, *10*, 759−768 and references therein. (e) Hotoda, H.; Murayama, K.; Miyamoto, S.; Iwata, Y.; Takahashi, M.; Kawase, Y.; Tanzawa, K.; Kaneko, M. Molecular recognition of adenophostin, a very potent Ca^{2+} inducer, at the D-*myo*-inositol 1,4,5-trisphosphate receptor, *Biochemistry* **1999**, *38*, 9234−9241.

(8) (a) Inoue, T.; Kikuchi, K.; Hirose, K.; Iino, M.; Nagano, T. Synthesis and evaluation of 1-positon-modified inositol 1,4,5-trisphosphate analogues. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1697−1702. (b) Inoue, T.; Kikuchi, K.; Hirose, K.; Iino, M.; Nagano, T. Small molecule-based laser inactivation of inositol 1,4,5-trisphosphate receptor. *Chem. Biol.* **2000**, *8*, 9−15. (c) Nakanishi, W.; Kikuchi, K.; Inoue, T.; Hirose, K.; Iino, M.; Nagano, T. Hydrophobic modifications at 1-phosphate of inositol 1,4,5-trisphosphate analogues enhance receptor binding. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 911−913.

(9) Davis, A. M.; Teague, S. J. Hydrogen bonding, hydrophobic interactions and failure of the rigid receptor hypothesis. *Angew. Chem., Int. Ed.* **1999**, *38*, 736−749.

(10) (a) Ahang, M.-Q.; Leurs, R.; Timmerman, H. Histamine H_1-receptor antagonists. In *Burger's medicinal chemistry and drug discovery*, 5th edition; Wolff, M. E., Eds.; John Wiley & Sons: New York, 1997; Vol. 5, pp 495−559. (b) Timmerman, H.; Smith, R. D. Major classes of currently established antihypertensive drugs. In *Burger's medicinal chemistry and drug discovery*, 5th edition; Wolff, M. E., Eds.; John Wiley & Sons: New York, 1997; Vol 2, pp 278−299.

(11) A preliminary account on the synthesis of **5a** has appeared: Mochizuki, T.; Kondo, Y.; Abe, H.; Taylor, C. W.; Potter, B. L. V.; Matsuda, A.; Shuto, S. Design and synthesis of 5′-deoxy-5′-phenyadenophostin A, a highly potent IP_3 receptor ligand. *Org. Lett.* **2006**, *8*, 1455−1458.

(12) Niedballa, U.; Vorbrüggen, H. A general synthesis of *N*-glycosides. I. Synthesis of pyrimidine nucleosides. *J. Org. Chem.* **1974**, *39*, 3654−3660.

(13) (a) Kahne, D.; Walker, S.; Cheng, Y.; Van Engen, D. Glycosylation of unreactive substrates. *J. Am. Chem. Soc.* **1989**, *111*, 6881−6882. (b) Yan, L.; Kahne, D. Generalizing glycosylation: synthesis of the blood group antigens Le^a, Le^b, and Le^x using a standard set of reaction conditions. *J. Am. Chem. Soc.* **1996**, *118*, 9239−9248.

(14) (a) Crich, D.; Sun, S. Formation of β-mannopyranosides of primary alcohols using the sulfoxide method. *J. Org. Chem.* **1996**, *61*, 4506−4507. (b) Crich, D.; Sun, S. Are glycosyl triflates intermediates in the sulfoxide glycosylation method? A chemical and ^1H, ^{13}C, and ^{19}F NMR spectroscopic investigation. *J. Am. Chem. Soc.* **1997**, *119*, 11217−11223.

(15) (a) Abe, H.; Shuto, S.; Matsuda, A. Highly α- and β-selective radical *C*-glycosylation reactions based on the conformational restriction strategy using a controlling anomeric effect. A study on the conformation-anomeric effect-stereoselectivity relationship in the anomeric radical reactions. *J. Am. Chem. Soc.* **2001**, *123*, 11870−11882. (b) Tamura, S.; Abe, H.; Matsuda, A.; Shuto, S. Control of the α/β-stereoselectivity in Lewis acid-promoted *C*-glycosidation using a controlling anomeric effect based on the conformational restriction strategy. *Angew. Chem., Int. Ed.* **2003**, *42*, 1021−1023. (c) Abe, H.; Terauchi, M.; Matsuda, A.; Shuto, S. A study on the conformation-anomeric effect-stereoselectivity relationship in anomeric radical reactions using conformationally restricted glucose derivatives as substrates. *J. Org. Chem.* **2003**, *68*, 7439−7447.

(16) (a) Montchamp, J. L.; Tian, F.; Hart, M. E.; Frost, J. W. Butane 2,3-bisacetal protection of vicinal diequatorial diols. *J. Org. Chem.* **1996**, *61*, 3897−3899. (b) Hense, A.; Ley, S. V.; Osborn, H. M. I.; Owen, D. R.; Poisson, J.-F.; Warriner, S. L.; Wesson, K. E. Direct preparation of diacetals from 1,2-diketones and their use as 1,2-diol protecting groups. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2023−2031.

(17) Parr, I. B.; Horenstein, B. A. New electronic analogues of the sialyl cation: *N*-functionalized 4-acetamido-2,4-dihidroxypiperidines. Inhibition of bacterial sialidases. *J. Org. Chem.* **1997**, *62*, 7489−7494.

(18) Nonstereoselective examples of Vorbrüggen glycosylation, see: Azuma, T.; Isono, K. Transnucleosidation: An improved method for transglycosylation from pyrimidines to purines. *Chem. Pharm. Bull.* **1977**, *25*, 3347−3353.

(19) Nomura, M.; Sato, T.; Washinosu, M.; Tanaka, M.; Asao, T.; Shuto, S.; Matsuda, A. Practical large-scale synthesis of 1-(3-*C*-ethynyl-β-*ribo*-pentofuranosyl)cytosine (ECyd), a potent antitumor nucleoside. Isobutyryloxy group as an efficient anomeric leaving group in the Vorbrüggen glycosylation reaction. *Tetrahedron* **2002**, *58*, 1279−1288.

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

(21) Hayakawa, Y.; Kataoka, M. Facile synthesis of oligodeoxyribonucleosides via the phosphoroamidite method without nucleoside base protection. *J. Am. Chem. Soc.* **1998**, *120*, 12395−12401.

(22) A review of organocopper reagents: Bruce, H. L.; Sengupta, S. Organocopper reagents: substitution, conjugate addition, carbo/metallocupration, and other reactions. *Org. React.* **1992**, *41*, 135−631.

(23) Kakefuda, A.; Shuto, S.; Nagahata, T.; Seki, J.; Sasaki, T.; Matsuda, A. Synthesis and biological evaluations of ring-expanded oxetanocin analogues: purine and pyrimidine analogues of 1,4-anhydro-2-deoxy-D-arabitol and 1,4-anhydro-2-deoxy-3-hydroxymethyl-D-arabitol. *Tetrahedron* **1994**, *50*, 10167−10182.

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

(25) Altona, C.; Sundaralingam, M. Conformational analysis of the sugar ring in nucleosides and nucleotides. Improved method for the interpretation of proton magnetic resonance coupling constants. *J. Am. Chem. Soc.* **1974**, *95*, 2333−2344.

(26) Preference of a C2′-*endo* form (C2′-*endo*/C3′-*endo* = ca. 7/3) in adenophostin A has been shown by the previous studies: ref 7e.

(27) Bosanac, I.; Alattia, J.-R.; Mal, T. K.; Chan, J.; Talarico, S.; Tong, F. K.; Tong, K. I.; Yoshikawa, F.; Furuichi, T.; Iwai, M.; Michikawa, T.; Mikoshiba, K.; Ikura, M. Structure of the inositol 1,4,5-trisphosphate receptor binding core in complex with its ligand. *Nature* **2002**, *420*, 696−700.

JM060310D