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Synthesis of the *C*-glycosidic analog of adenophostin A, a potent IP_3 receptor agonist, using a temporary silicon-tethered radical coupling reaction as the key step[1]

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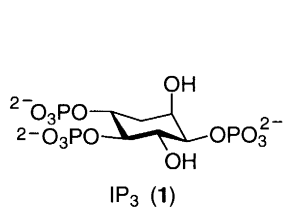
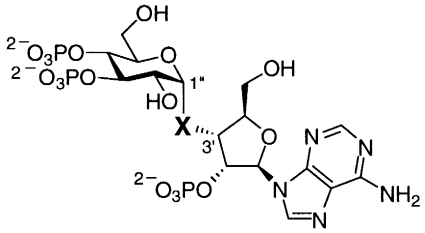
Abstract

Synthesis of the *C*-glycosidic analog (**3**) of adenophostin A, a very potent IP_3 receptor agonist, was achieved using a temporary silicon-tethered reductive radical coupling reaction as the key step. Radical reaction of the silaketal substrate **6** with Bu_3SnH/AIBN in benzene occurred stereoselectively, and subsequent desilylation gave the desired *C*-glycosidic disaccharide **7** with the (3α,1′α)-configuration as the major product. Compound **7** was converted into the target **3** via the introduction of an adenine base by a Vorbrüggen glycosylation reaction.

Considerable 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.[2,3] Therefore, much effort has been devoted to the development of specific ligands for the IP_3 receptors, which are very useful for proving the mechanism of IP_3-mediated Ca^{2+} signaling pathways.[4] Recently, adenophostin A (**2**) was isolated from *Penicillium brevicompactum* by Takahashi and co-workers and identified as the strongest IP_3 receptor ligand yet known; **2** is 10–100 times more potent than IP_3 with regard to both the affinity for the IP_3 receptor and the Ca^{2+}-mobilizing ability in cells.[5] This finding prompted us to synthesize the *C*-glycosidic analog **3** of adenophostin A and to examine its biological features,[6] since *C*-glycosides are known as useful mimics of carbohydrates by enhancing their stability.[7]



IP3 (1)



2: X = O (adenophostin A)
3: X = CH_2

In the synthesis of the target compound **3**, the key step is the formation of the *C*-glycosidic linkage with the desired (3′α,1′′α)-configuration, as shown in our synthetic plan in Scheme 1. The key *C*-glycosidic

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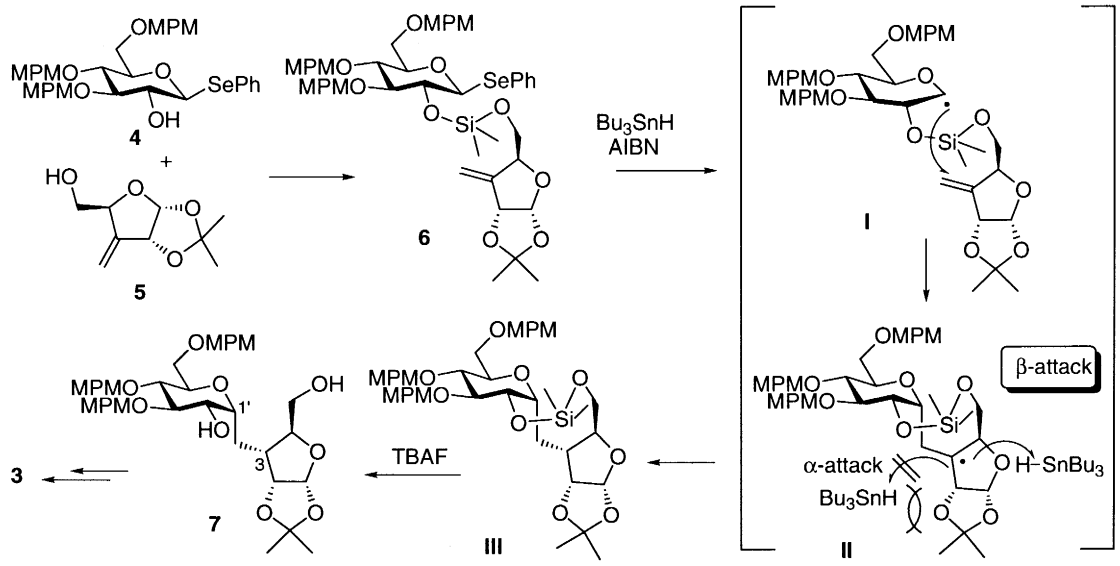
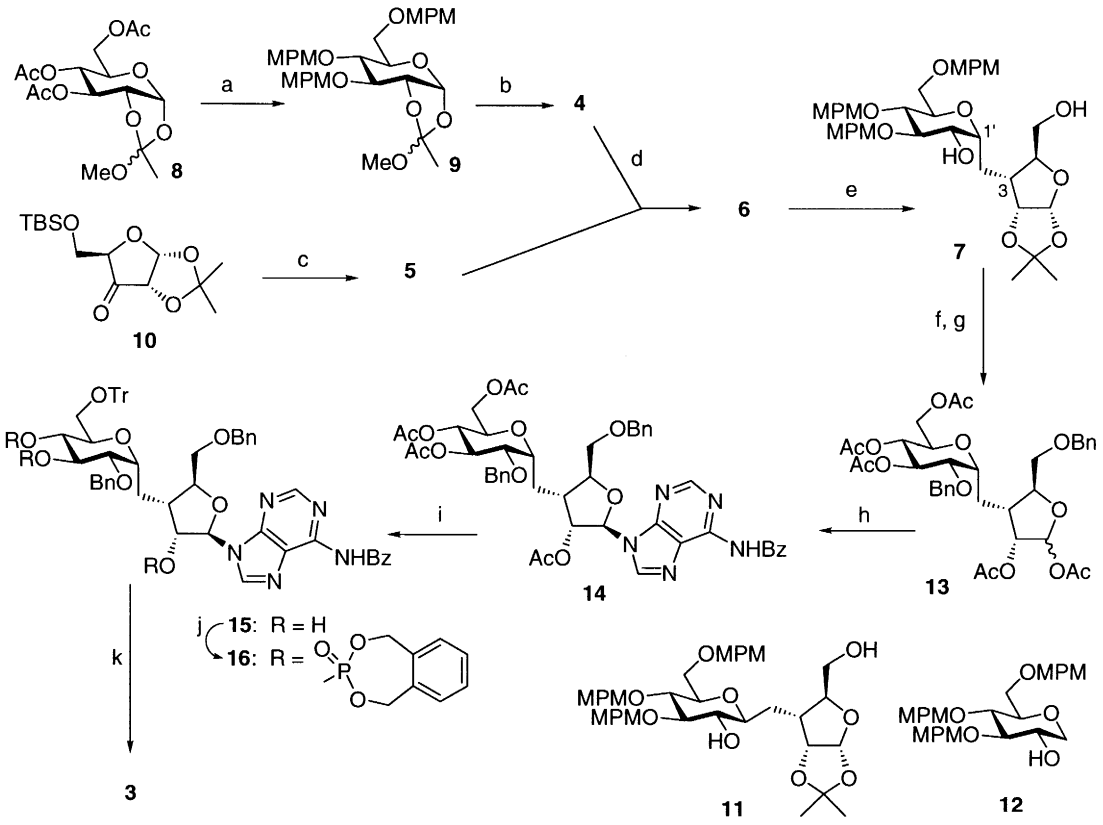
linkage is constructed by a reductive radical coupling reaction of the silaketal tethered[8] substrate **6**, which can be prepared from the pyranose unit **4** and the furanose unit **5**. We assumed that treatment of **6** with Bu_3SnH/AIBN would produce the 1′-radical **I** in a boat conformation, and that its 1′α-selective cyclization[9] would occur at the sterically unhindered *endo*-position of the 3-methylene to give 3-radical **II**. Subsequent reduction by Bu_3SnH would occur stereoselectively from the β-face, due to the significant steric repulsion for the isopropylidene group when the reagent approaches the 3-position from the α-face. Accordingly, this radical reaction should proceed stereoselectively to give **III**, and subsequent desilylation would give **7** with the desired (3α,1′α)-configuration. From **7**, the target compound **3** can be synthesized via the introduction of an adenine base by Vorbrüggen's procedure.[10]



Scheme 1.

The synthesis of **3** is summarized in Scheme 2. Removal of the acetyl groups of the known orthoester **8**,[11] which was readily prepared from D-glucose, and subsequent protection of the resulting hydroxyls with *p*-methoxybenzyl (MPM) groups gave **9**. A PhSe group was introduced at the anomeric β-position by treating **9** with PhSeH/MS3Å,[12] and the resulting 2-*O*-acetyl group was removed to complete the synthesis of pyranose unit **4**. On the other hand, a Wittig reaction of a 3-keto sugar **10**,[13] prepared from D-xylose, with $Ph_3P{=}CH_2$ in THF gave the corresponding 3-methylene product, the 5-*O*-TBS group of which was removed with TBAF to give the furanose unit **5**. Next, the units **4** and **5** were temporarily connected with a silaketal linkage. Thus, treatment of **4** with BuLi/Me_2SiCl_2 in THF yielded the corresponding 2-*O*-Si(Cl)Me_2 product, which was then treated with **5** in the presence of Et_3N to give the silaketal **6**, the substrate for the radical coupling reaction, in 67% yield.

Next, the reductive coupling reaction of **6** was investigated with Bu_3SnH/AIBN. When a solution of Bu_3SnH (2.0 equiv.) and AIBN (0.5 equiv.) in benzene was added slowly over 1.2 h to a solution of **6** in benzene at 80°C, the best results were observed. After the reaction mixture was treated with Bu_4NF in THF and purified by silica gel flash chromatography, the desired (3α,1′α)-*C*-glycoside **7**[14] was obtained as the major product (50%) along with the *C*-glycoside **11** having the (3α,1′β)-configuration (22%) and the directly reduced product **12** (25%). After protection of the two free hydroxyls of **7** with the benzyl groups, the MPM groups were removed with 90% TFA, and the resulting free hydroxyls were acetylated to give **13**. N^6-Benzoyladenine was successfully introduced at the 1β-position of **13**, using the usual Vorbrüggen glycosylation procedure with a silylated base and $SnCl_4$ in MeCN to give adenyl *C*-disaccharide **14** in 65% yield. The four acetyl groups of **14** were removed simultaneously, and the 6′′-



Scheme 2. Reagents and conditions: (a) (1) NaOMe, THF/MeOH, rt; (2) NaH, MPMCl, HMPA/DMF, rt, 77%; (b) (1) PhSeH, MS3Å, $MeNO_2$, reflux; (2) NaOMe, THF/MeOH, rt, 65%; (c) (1) $NaOCMe_2Et$, Ph_3PMeBr, THF, rt; (2) TBAF, THF, rt, 80%; (d) (1) Me_2SiCl_2, BuLi, THF, −78°C–rt; (2) **5**, Et_3N, THF, 0°C–rt, 67%; (e) (1) Bu_3SnH, AIBN, benzene, reflux; (2) TBAF, THF, 50%; (f) BnBr, NaH, HMPA/DMF/THF, 0°C–rt, 72%; (g) (1) 90% TFA, 0°C–rt; (2) NaOMe, MeOH, rt; (3) Ac_2O, Et_3N, DMAP, MeCN, 70%; (h) silylated N^6-benzoyladenine, $SnCl_4$, MeCN, 0°C–rt, 65%; (i) (1) NaOMe, MeOH; (2) TrCl, py, 0–50°C, 95%; (j) XEPA, CH_2Cl_2, −40°C, then *m*-CPBA, −40°C–rt, 92%; (k) (1) NH_3, aq. dioxane, rt; (2) H_2, Pd-black, aqueous MeOH, rt, 89%

primary hydroxyl was selectively protected by a trityl group to give **15**. Phosphate units were introduced, using the phosphoramidite method with *o*-xylene *N*,*N*-diethylphosphoramidite (XEPA) developed by Watanabe and co-workers.[15] Thus, **15** was treated with XEPA and tetrazole in CH_2Cl_2, followed by oxidation with *m*-CPBA to give the desired 2′,3′′,4′′-trisphosphate derivative **16** in 92% yield. The N^6-benzoyl group was removed with NH_3/aq. dioxane. Finally, the trityl- and benzyl-protecting groups were all removed in one step by catalytic hydrogenation with Pd-black in aqueous MeOH to give the target compound **3** in 89% yield as a sodium salt, after treatment with ion-exchange resin.

In summary, we have successfully synthesized the *C*-glycosidic analog **3** of adenophostin A, using a temporary silicon-tethered reductive coupling reaction as the key step.[16] Biological evaluation of **3** is under investigation and will be reported elsewhere.

Acknowledgements

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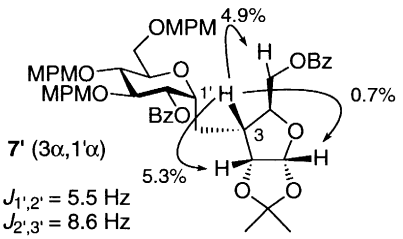

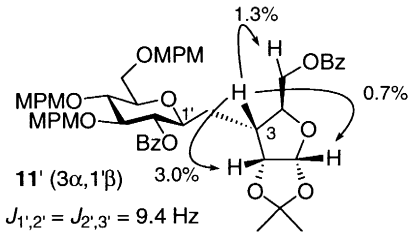

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