

Synthesis of the C-glycosidic analog of adenophostin A, a potent IP₃ receptor agonist, using a temporary silicon-tethered radical coupling reaction as the key step¹

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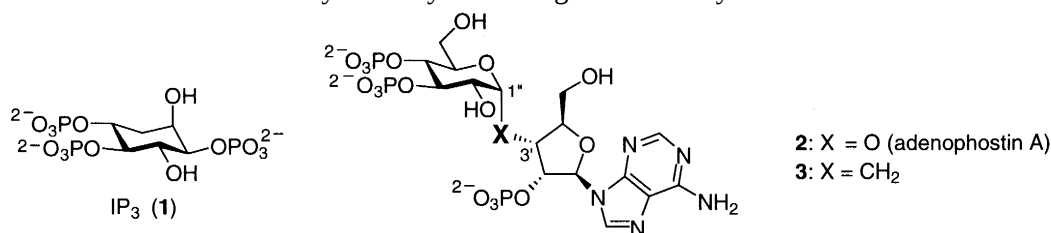
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Abstract

Synthesis of the C-glycosidic analog (**3**) of adenophostin A, a very potent IP₃ 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 Bu₃SnH/AIBN in benzene occurred stereoselectively, and subsequent desilylation gave the desired C-glycosidic disaccharide **7** with the (3 α ,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. © 2000 Elsevier Science Ltd. All rights reserved.

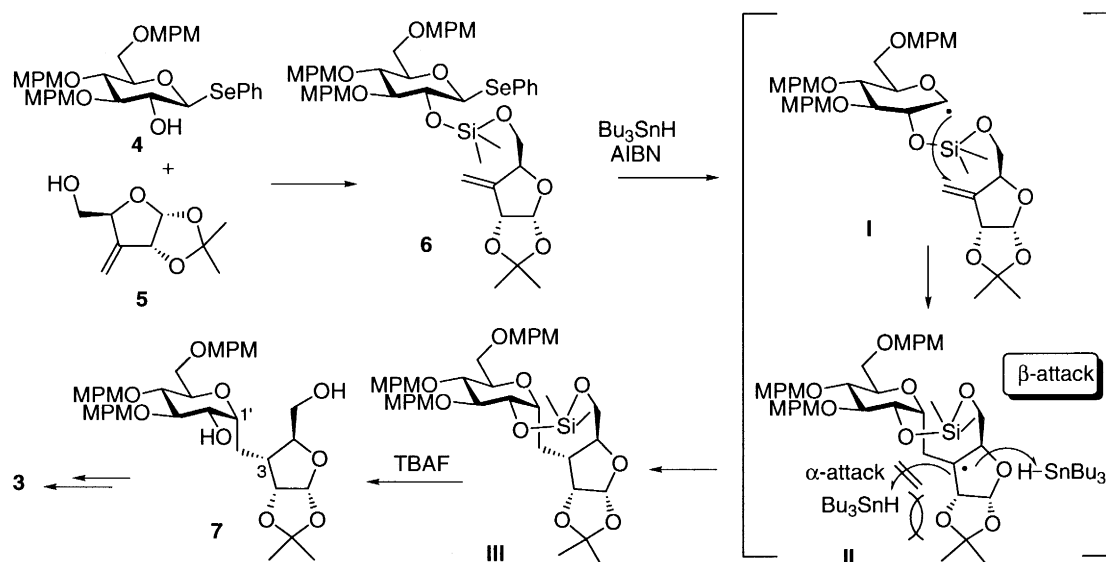
Considerable attention has been focused on D-*myo*-inositol 1,4,5-trisphosphate (IP₃, **1**), an intracellular Ca²⁺-mobilizing second messenger, because of its biological importance.^{2,3} Therefore, much effort has been devoted to the development of specific ligands for the IP₃ receptors, which are very useful for proving the mechanism of IP₃-mediated Ca²⁺ signaling pathways.⁴ Recently, adenophostin A (**2**) was isolated from *Penicillium brevicompactum* by Takahashi and co-workers and identified as the strongest IP₃ receptor ligand yet known; **2** is 10–100 times more potent than IP₃ with regard to both the affinity for the IP₃ receptor and the Ca²⁺-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



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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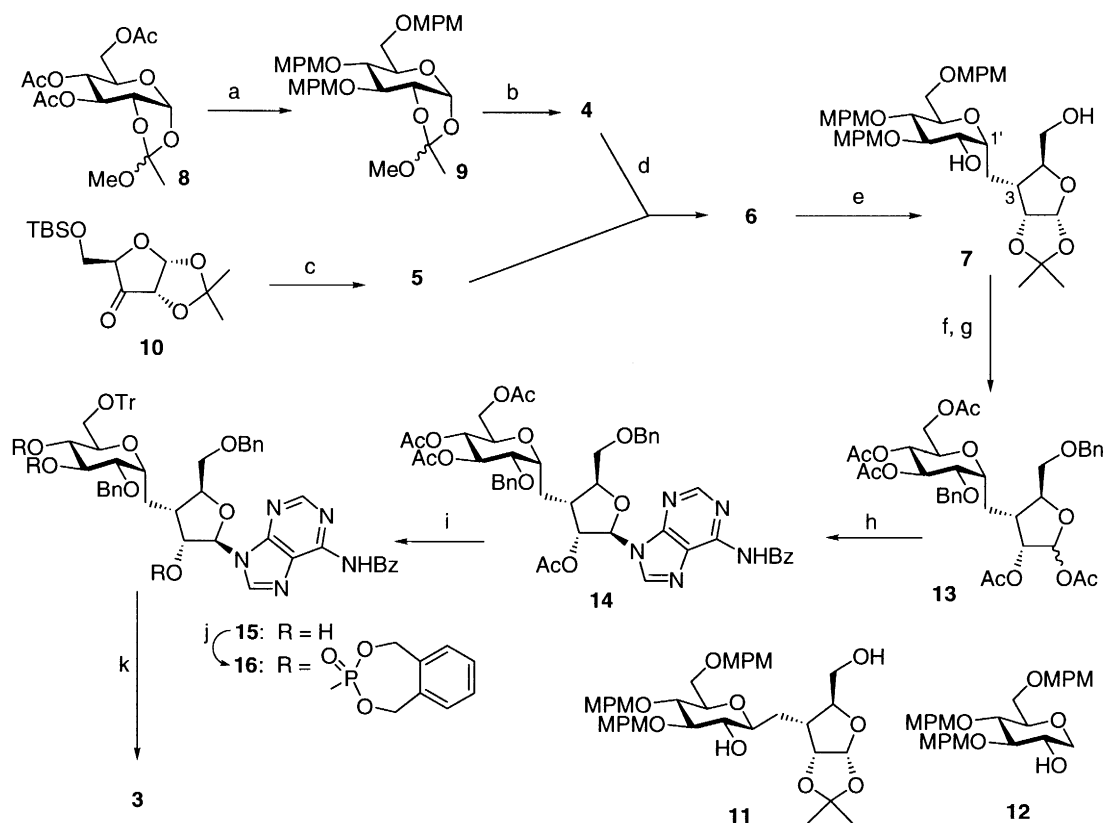
linkage is constructed by a reductive radical coupling reaction of the silaketal tethered⁸ substrate **6**, which can be prepared from the pyranose unit **4** and the furanose unit **5**. We assumed that treatment of **6** with Bu₃SnH/AIBN would produce the 1'-radical **I** in a boat conformation, and that its 1'α-selective cyclization⁹ would occur at the sterically unhindered *endo*-position of the 3-methylene to give 3-radical **II**. Subsequent reduction by Bu₃SnH 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 Ph₃P=CH₂ 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/Me₂SiCl₂ in THF yielded the corresponding 2-O-Si(Cl)Me₂ product, which was then treated with **5** in the presence of Et₃N 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 Bu₃SnH/AIBN. When a solution of Bu₃SnH (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 Bu₄NF 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**. N⁶-Benzoyladenine was successfully introduced at the 1β-position of **13**, using the usual Vorbrüggen glycosylation procedure with a silylated base and SnCl₄ in MeCN to give adeny 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, MS3A, MeNO₂, reflux; (2) NaOMe, THF/MeOH, rt, 65%; (c) (1) NaOCMe₂Et, Ph₃PMeBr, THF, rt; (2) TBAF, THF, rt, 80%; (d) (1) Me₂SiCl₂, BuLi, THF, -78°C–rt; (2) 5, Et₃N, THF, 0°C–rt, 67%; (e) (1) Bu₃SnH, 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) Ac₂O, Et₃N, DMAP, MeCN, 70%; (h) silylated N⁶-benzoyladenine, SnCl₄, MeCN, 0°C–rt, 65%; (i) (1) NaOMe, MeOH; (2) TrCl, py, 0–50°C, 95%; (j) XEPA, CH₂Cl₂, -40°C, then *m*-CPBA, -40°C–rt, 92%; (k) (1) NH₃, aq. dioxane, rt; (2) H₂, 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 CH₂Cl₂, followed by oxidation with *m*-CPBA to give the desired 2',3'',4''-trisphosphate derivative **16** in 92% yield. The N⁶-benzoyl group was removed with NH₃/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.

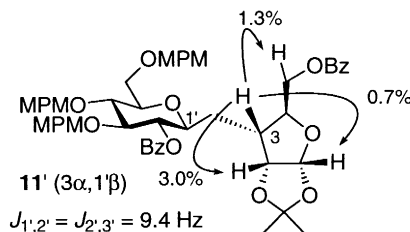
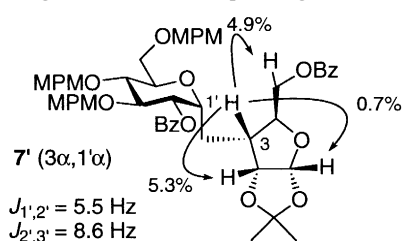
In summary, we have successfully synthesized the C-glycosidic analog **3** of adenophostin A, using a temporary silicon-tethered reductive coupling reaction as the key step.¹⁶ Biological evaluation of **3** is under investigation and will be reported elsewhere.

Acknowledgements

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