Synthesis of An Elicitor-Active Hexaglucoside Analogue by a One-Pot, Two-Step Glycosidation Procedure

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The elicitor-active hexa-β-D-glucopyranosyl-D-glucitol (**1**), isolated from mycelial walls of *Phytophthora megasperma* f.sp. glycinea, induces antibiotic phytoalexin accumulation in soybeans.[1,2] Biological assays of several oligoglucosides revealed that hexa-β-glucoside **2** is the minimum structural element required for high elicitor activity.[3] Presumably this hexaglucoside has a specific structure to trigger the signal transduction pathway, leading to the synthesis of phytoalexins in soybeans. Methods to construct glycosidic linkages have made considerable progress as a result of the development of glycosidation procedures.[4] There are a few general methodologies directed to the synthesis of oligosaccharides, such as solid-phase synthesis,[5] one-step synthesis,[6] enzyme-assisted synthesis,[7] two-stage activation procedure,[8] armed/disarmed glycosidation,[9] and silicon-connected glycosidation.[10] We report here the application of a one-pot, two-step glycosidation to the synthesis of an elicitor-active hexaglucoside **3**.

The one-pot approach arose from the idea that if the difference in reactivity between glycosyl donor **4** (X_1) and acceptor **5** (X_2) is large enough to be distinguished by the activator A_1, then the glycosyl donor **4** can be selectively activated in the presence of A_1 to give the tetraglucoside **6** (Figure 1). Subsequent activation of X_2 in **6** in the presence of another activator A_2, followed by coupling with the glycosyl acceptor **7**, would provide the hexaglucoside **3** by a one-pot procedure. In our method for the one-pot glycosidation, it is expected that the initial coupling of glycosyl trichloroacetimidate **4** (X_1 = O(CNH)CCl_3)[11] with

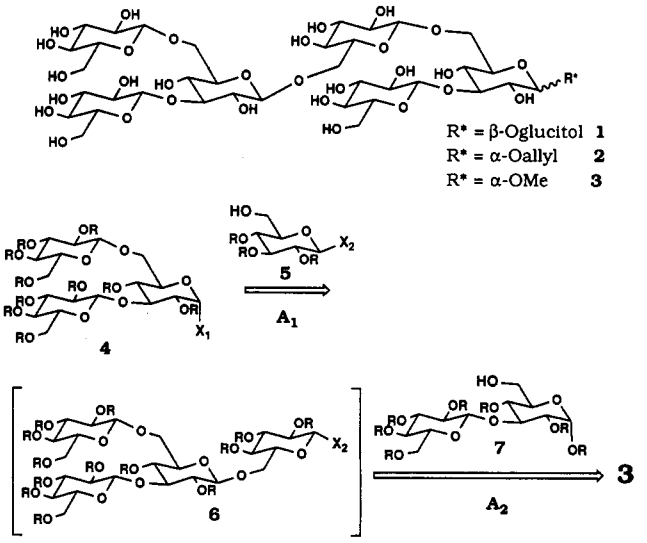

Figure 1.

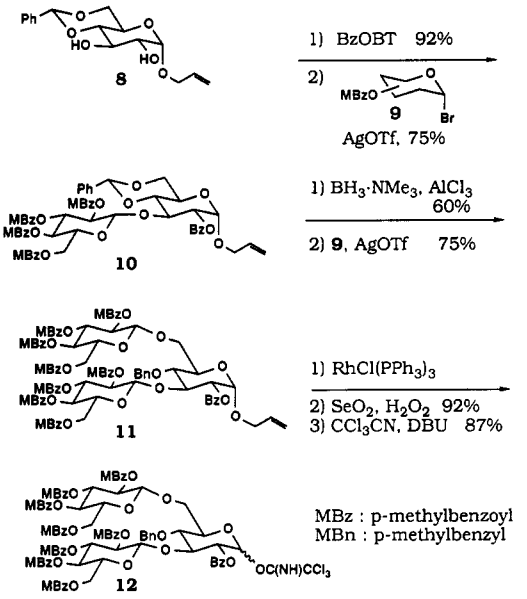

Figure 2.

thioglycoside **5** (X_2 = SPh)[12] in the presence of a catalytic amount of activator A_1 (TMSOTf)[13] would give **6**. While the anomeric phenylthio groups in **5** and **6** are stable to the TMSOTf activation, addition of a second activator, A_2 (NIS),[14] and glycosyl acceptor **7** to the reaction mixture should promote the selective activation of the glycosyl donor **6** to give the hexaglucoside **3** in one pot. In this reaction, TfOH generated at the first stage is effectively used for the second glycosidation step (TfOH/NIS).

At first, triglucoside **12** was synthesized as the initial glycosyl donor **4** in the following way (Figure 2). Allyl glucoside (**8**) was prepared in 50% yield from glucose by treatment with allyl alcohol and Amberlite IR-120 (H^+) resin, followed by benzylidenation with benzaldehyde dimethyl acetal. Selective protection of the 2-hydroxy group in **8** with BzOBT[15] gave a 92% yield of the 3-hydroxyglucoside, which was subjected to glycosidation with

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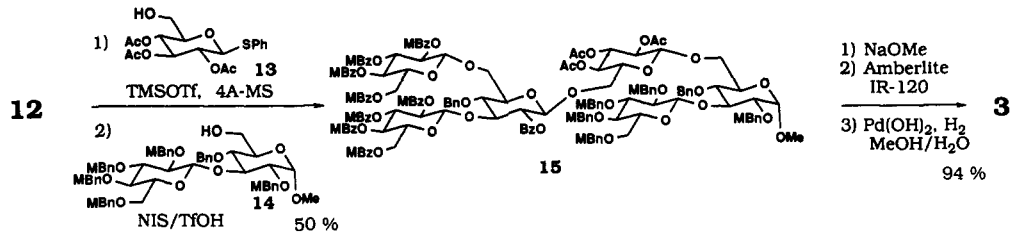

Figure 3.

permethylbenzoyl glucosylbromide (**9**) in the presence of AgOTf[16] to afford the α-diglucoside **10** in 75% yield. Reductive ring opening of **10** with $BH_3{\cdot}NMe_3$ and $AlCl_3$[17] resulted in the formation of the 6-hydroxydiglucoside in 60% yield. Glycosidation of the resulting alcohol was carried out with **9** in the presence of AgOTf to give triglucoside **11** in 75% yield. Removal of the 1-*O*-allyl group by treatment with $RhCl(PPh_3)_3$ followed by hydrolysis of the vinyl ether with SeO_2 and H_2O_2 gave the 1-*O*-unprotected triglucosides. Isomerization of the anomeric alcohol was observed during hydrolysis of the vinyl ether. Treatment of both triglucosides with CCl_3CN and DBU afforded the ca. 10:1 mixture of α- and β-trichloroacetimidate **12** in 87% yield.

One-pot glycosidation of the trichloroacetimidate **12**, the phenylthioglucoside **13**, and the acceptor **14**[18] was then examined. (Figure 3) Selective activation of imidates **12** (α/β mixture) with **13** and 4-Å molecular sieves by treatment with a catalytic amount of TMSOTf in CH_2Cl_2 at room temperature resulted in the formation of the phenylthiotetraglucoside. To the reaction mixture was added the acceptor **14**, and then the phenylthio group was activated by treatment with NIS (5 equiv) and TfOH to give hexaglucoside **15** in 50% yield. Treatment of **15** with NaOMe in MeOH and subsequent neutralization with Amberlite IR-120 gave the benzyl ether, which was hydrogenolyzed over palladium hydroxide on carbon in MeOH and H_2O to afford the desired hexaglucoside **3** in 94% overall yield.

In conclusion, we have developed a new method to incorporate multiple glycosidic linkages into oligosaccharides. The ability to control the reactivity of the glycosyl donors suggests a novel strategy for the synthesis of oligosaccharides in a one-pot reaction. Extension of this one-pot concept could, in principle, form the basis for an automated carbohydrate synthesizer.

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Supplementary Material Available: Synthesis of **12** and **14** and experimental procedure for the one-pot glycosidation (11 pages). This material is contained in many 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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(18) Details of the synthesis of diglucoside **14** are available as supplementary material.