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Stereoselective synthesis of β-glycosyl esters of *cis*-cinnamic acid and its derivatives using unprotected glycosyl donors

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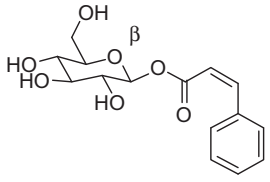
ABSTRACT

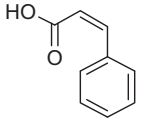
The β-glycosyl esters of *cis*-cinnamic acid were synthesized directly using Hannesian's unprotected glycosyl donor and the carboxylic acid in toluene. This protocol does not require protecting groups on the glycosyl donors, and high stereoselectivity was achieved. The first synthesis of a potent allelochemical, 1-*O*-*cis*-cinnamoyl-β-D-glucopyranose, is also described.

Some plants are known to produce growth-regulating compounds, which when released into the environment, affect the growth and development of other plants. This phenomenon is defined as allelopathy and the related bioactive compounds are called allelochemicals. Allelochemicals are expected to be an integral part of the design of potent, environmentally safe herbicides in the future.[1] In 2004, Hiradate and Fujii isolated 1-*O*-*cis*-cinnamoyl-β-D-glucopyranose (**1**) and identified it as a potent allelochemical derived from *Spiraea thunbergii*.[2] They proposed that the *cis*-cinnamic acid (**2**) might be an essential structure for inhibition, since both **2** and the glycoside **1** inhibit the lettuce root growth at a comparable level (Fig. 1). The glycoside **1** would be readily transformed into **2** in soil and/or by microorganisms due to the lability of the glycosyl ester moiety.

For the confirmation of the structure, a structure–activity relationship study, and a plant physiological study of the natural product, the chemical synthesis of a sufficient amount of the glycosyl ester and its derivatives would be required. Although many kinds of glycosyl esters are present in nature, their chemical synthesis has been problematic, because the glycosyl esters are much more labile than glycosyl ethers. To achieve a regioselective, efficient synthesis of the glycosides, suitable protection of the hydroxyl groups, which do not participate in the glycosylation, is usually required, but subsequent deprotection under acidic or basic conditions would likely cause the cleavage of the glycosyl ester. Furthermore, in the present case, catalytic hydrogenation or Birch-type reduction for the removal of the benzylic protecting groups cannot be employed since the carbon–carbon double bond of the cinnamate might be damaged in the process. Appropriate deprotection conditions, namely mild enough so as not to cleave and/or migrate the ester, have not been developed for this particular system. After numerous unsuccessful attempts to deprotect the protected glycosyl ester **3** to give the unprotected β-glycosyl *cis*-cinnamic acid ester **1** (Scheme 1), we decided to use the unprotected glycosyl donors,



1-O-*cis*-Cinnamoyl-β-D-glucopyranose (**1**)



cis-Cinnamicacid (**2**)

Figure 1. The natural allelochemical **1** and the proposed essential structure **2** for its bioactivity.

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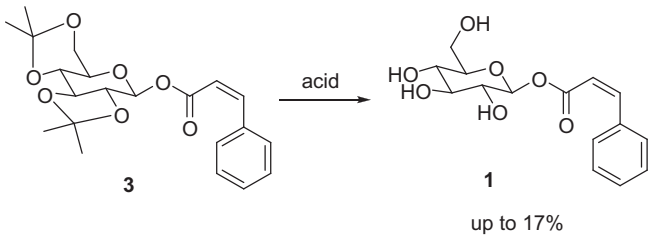
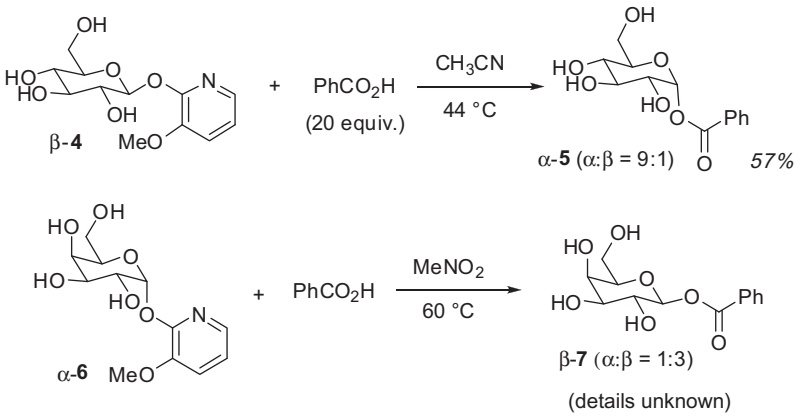


Scheme 1. Attempts to deprotect the β-D-glycosyl ester.

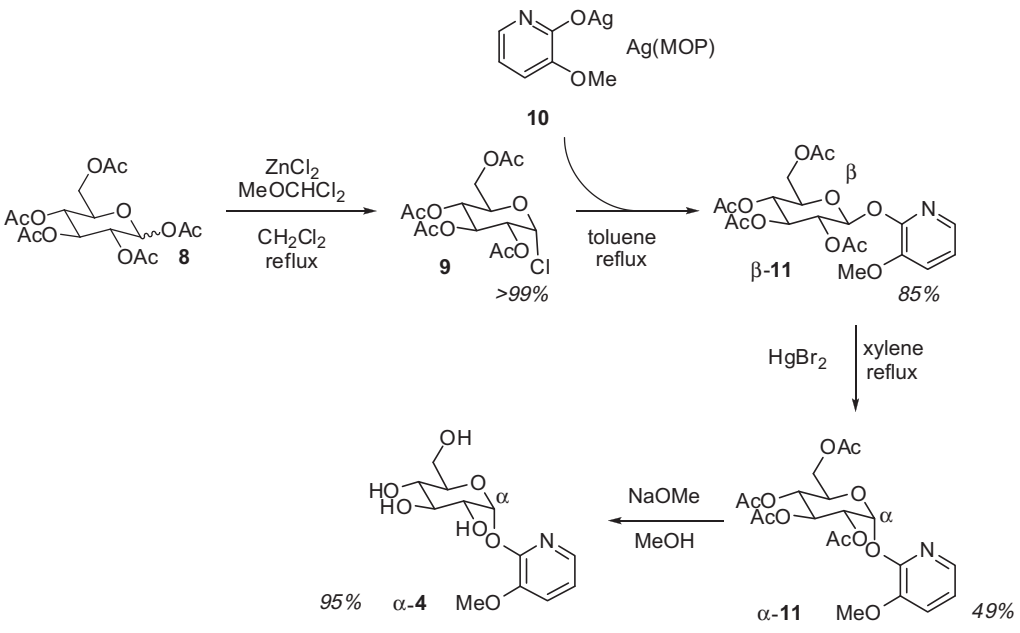
very few of which have been reported.[3] For example, Hannesian and coworkers reported the stereoselective synthesis of the α-glycosyl esters using 2-(methoxypyridyl) D-hexopyranoside **4** as an unprotected glycosyl donor (Scheme 2).[4] However, they only briefly described the β-glycosylation that was employed with benzoic acid and α-2-methoxypyridyl galactopyranoside **6** in nitromethane to provide a 1:3 (α:β) ratio.[4f] Although the key point seems to be suppression of the α−β interconversion of the glycosyl donor by the solvent, the selective synthesis of the β-glycosyl esters using unprotected glycosyl donors has not been established so far. Herein, we report the first selective synthesis of the glycoside **1** via the β-glycosyl esterification of an unprotected glycosyl donor via a modified Hannesian protocol.

In order to obtain the β-glycosyl esters selectively, the α-2-(methoxypyridyl) D-glucopyranoside **4** was prepared according to the literature. As shown in Scheme 3, tetra-*O*-acetyl-β-D-glucopyranose **8** was converted into the glycosyl α-chloride **9**,[5] which was then treated with silver 3-methoxy-2-pyridoxide **10**, prepared from the 2-hydroxypyridine and silver nitrate, to afford the β-D-glucopyranosyl donor **11** in a good yield.[4e] The anomerization of β-**11** was carried out using $HgBr_2$ at high temperature to give the α-donor (α-**11**).[4a,4d,6] Deacetylation was effected via methanolysis to afford α-2-methoxypyridyl glucopyranoside **4** in a good yield.[6]

With the unprotected α-glycosyl donor in hand, we then examined the glycosylation of *cis*-cinnamic acid (**2**) (Table 1). According to the Hannesian's protocol, the glycosylation was performed in nitromethane as the solvent at 60 °C to give a 1:1 α/β mixture of the glycoside **1** quantitatively (entry 1). In DMF as a polar solvent, the undesired α-**1** predominated (entry 2), since the reaction probably proceeded through an intermediate such as an oxonium



Scheme 2. Hannesian glycosylation in the preparation of the α- and β-glycosyl esters.



Scheme 3. Synthesis of α-2-(methoxypyridyl) D-glucopyranoside **4**.