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

Kazumasa Matsuo [a], Keisuke Nishikawa [b], Mitsuru Shindo [b,*]

[a] Interdisciplinary Graduate School of Engineering Sciences, Kyushu University, Japan
[b] Institute for Materials Chemistry and Engineering, Kyushu University, 6-1, Kasugako-en, Kasuga 816-8580, Japan

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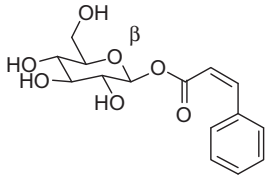
ABSTRACT

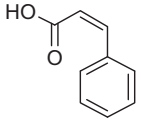
The β-glycosyl esters of *cis*-cinnamic acid were synthesized directly using Hannesian's unprotected glycosyl donor and the carboxylic acid in toluene. This protocol does not require protecting groups on the glycosyl donors, and high stereoselectivity was achieved. The first synthesis of a potent allelochemical,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

* Corresponding author.
E-mail address: shindo@cm.kyushu-u.ac.jp (M. Shindo).

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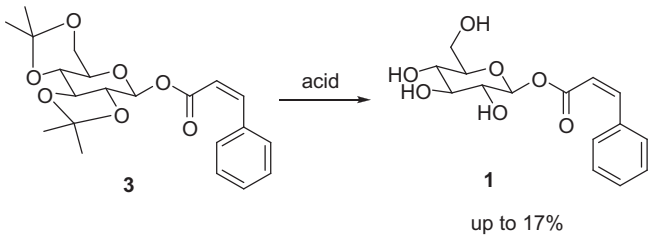
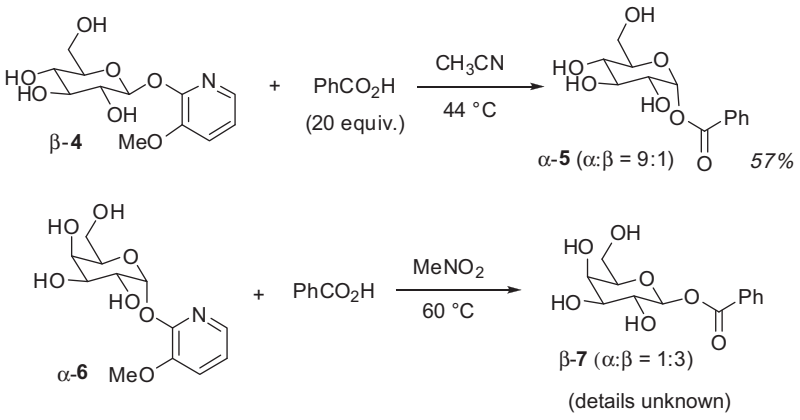


Scheme 1. Attempts to deprotect the β-D-glycosyl ester.

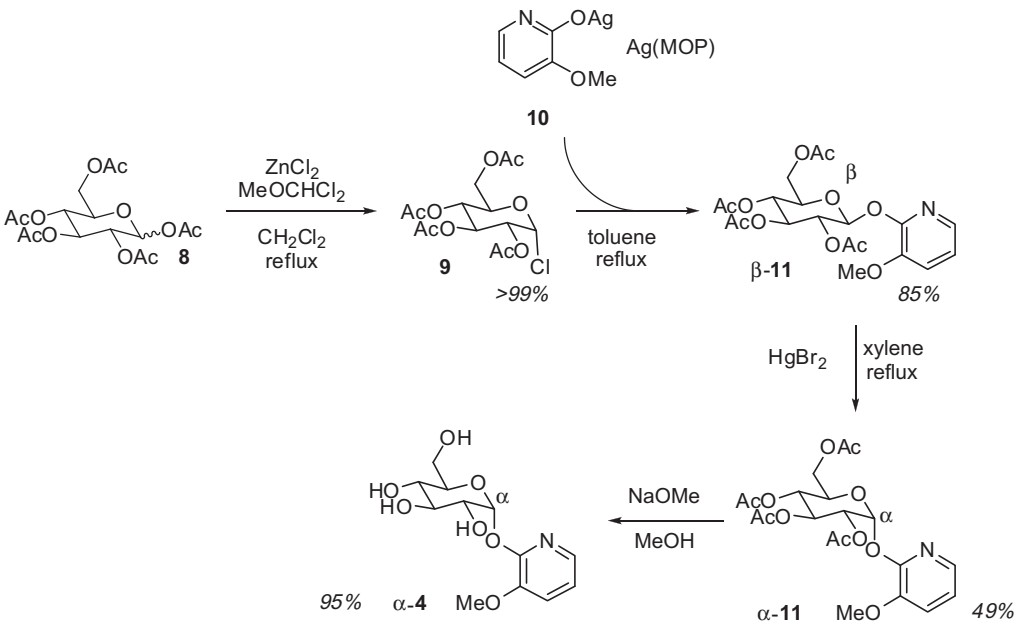
very few of which have been reported.[3] For example, Hannesian and coworkers reported the stereoselective synthesis of the α-glycosyl esters using 2-(methoxypyridyl) D-hexopyranoside **4** as an unprotected glycosyl donor (Scheme 2).[4] However, they only briefly described the β-glycosylation that was 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

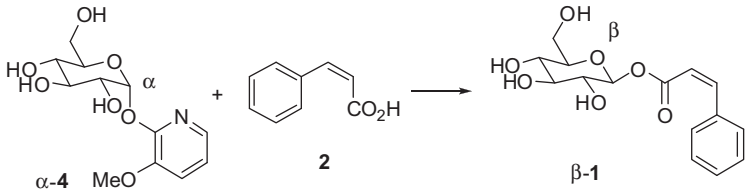


Scheme 2. Hannesian glycosylation in the preparation of the α- and β-glycosyl esters.



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

Table 1
Synthesis of the β-D-glycoside of *cis*-cinnamic acid (**2**)



Entry	Solvent	**2** (equiv)	**4** (M)	Temperature (°C)	Time (h)	α:β	Yield (%)
1	$MeNO_2$	20	0.035	60	3	1:1	>99
2	DMF	100	0.035	65	3	2:1	89
3	CH_3CN	20	0.035	44	16	1:2	98
4	Dioxane	20	0.035	101	4	1:2.9	74
5	CH_2Cl_2	20	0.035	30	48	1:4.0	79
6	Toluene	20	0.035	100	0.25	1:3.5	65[a]
7	Toluene	20	0.035	70	3	1:8.5	52[a]
8	Toluene	100	0.0035	70	8	1:15	91

[a] The byproducts **12** and **13** were obtained.

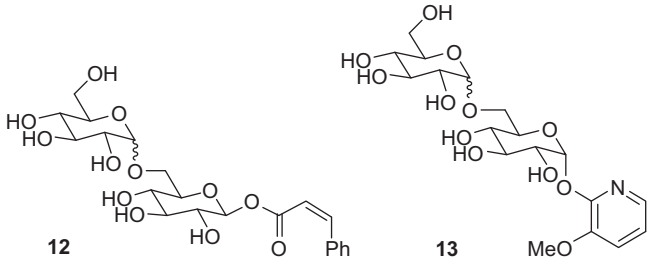
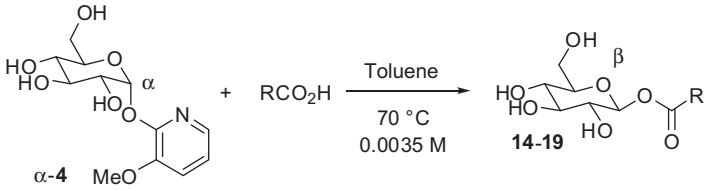


Table 2
Synthesis of the β-D-glycosides of several carboxylic acids



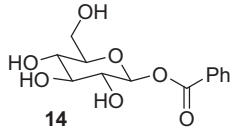
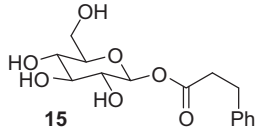
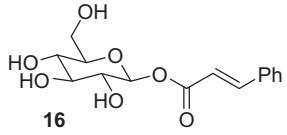
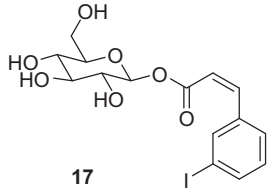
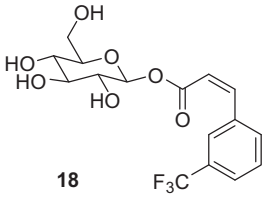
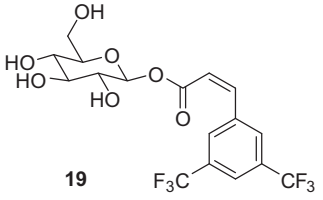
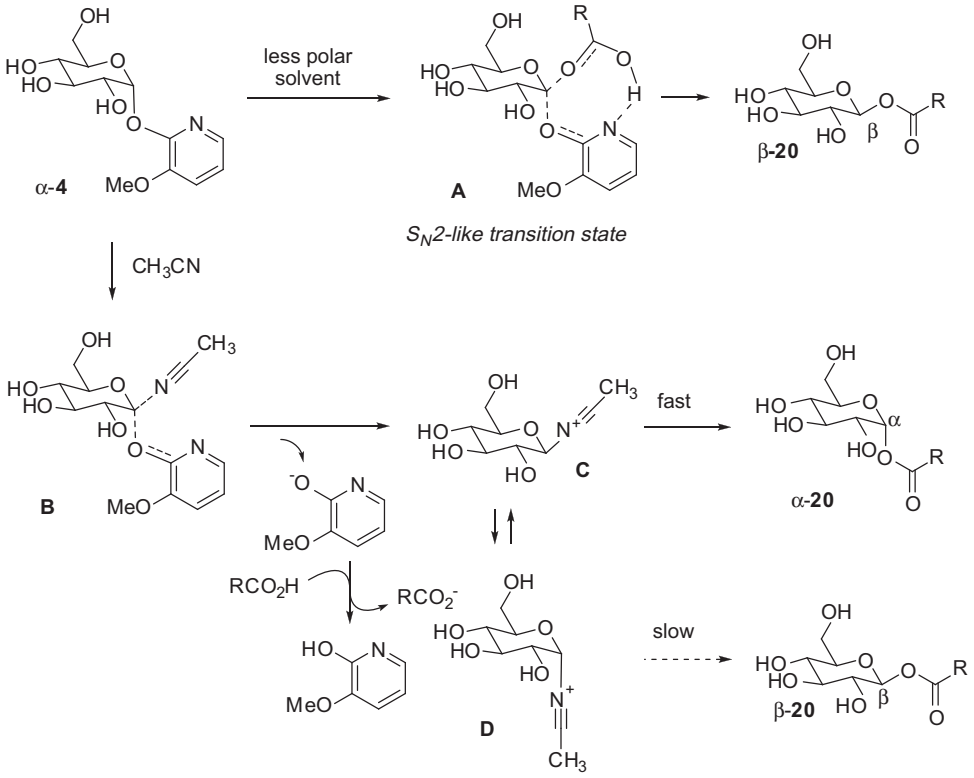
Entry	Products	Time (h)	α:β	Yield (%)
1	 **14**	16	1:13	67
2	 **15**	8	1:20	62
3	 **16**	16	1:14	61
4	 **17**	8	1:8	89

Table 2 (*continued*)

Entry	Products	Time (h)	α:β	Yield (%)
5	 **18**	8	1:11	91
6	 **19**	8	1:19	98

ion. However, with acetonitrile and dioxane as the solvent, the ratio was reversed to 1:2 and 1:2.9, respectively, in favor of the desired β-anomer (entries 3 and 4). In dichloromethane, although the reaction was sluggish due to the low boiling point, the β/α ratio increased up to 4 (entry 5). Less polar solvents would be expected to improve the ratio because solvent participation could be minimized. By using the much less polar solvent toluene at 100 °C, the ratio was 1:3.5 (entry 6), and at the lower temperature of 70 °C, a better ratio (1:8.5) was obtained in modest yield (entry 7), in which disaccharides, such as **12** and **13**, were detected by ESI-MS as side products (entries 6 and 7). To avoid this dimerization, the reaction was carried out under high-dilution conditions using 100 equiv of **2** to achieve an excellent yield of β-**1** and a



Scheme 4. Presumed mechanism of the glycosylation using the 2-methoxypyridyl group as the leaving group.[4f]

much better ratio of 1:15 (entry 8),[7] and the excess **2** was recovered quantitatively. Due to the instability of the product, which seems to decompose gradually in aqueous solution, the final purification was troublesome, for example, HPLC using an ODS column resulted in decomposition, but using a normal phase HPLC column with chloroform–methanol eluent to remove a mixture of the α-isomer and other impurities, the pure compound was successfully obtained. The spectra of **1** were identical with those of the natural product.

To show the generality of this method, several carboxylic acids were subjected to the β-glycosylation to afford the β-glucopyranosyl esters. As shown in Table 2, the β-glucosides of benzoic acid (entry 1), 3-phenylpropionic acid (entry 2), *trans*-cinnamic acid (entry 3), and the *cis*-cinnamic acid analogues were obtained in good yield with excellent β-selectivity (entries 4–6).

According to Hannesian's description of the mechanism of the glycosylation by 2-methoxypyridyl group as a leaving group,[4f] the α-glycosyl esterification would be promoted by protonation of the pyridyl moiety by the nucleophile (the carboxylic acid) and a subsequent S_N2-like reaction by the carboxylate would result in the formation of the β-glycosyl ester (Scheme 4). When a relatively polar solvent like acetonitrile was used, the intermediate **C** would be partially generated through the transition state **B**, and the resulting **C** and the anomer **D** would be in rapid equilibrium. Since the α-anomer **D** would react with the nucleophile slower than the β-anomer **C**, the α-glycosyl ester would also be generated based on the Curtin–Hammett principle.

In conclusion, we have achieved the first efficient synthesis of the potent allelochemical, the β-glycosyl ester of *cis*-cinnamic acid, by means of the stereoselective glycosylation using unprotected glycosyl donors via a modified Hannesian protocol. This method has high generality and is very useful for the synthesis of bioactive β-glycosyl esters in the structure–activity relationship studies.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.104.

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6. Preparation of α-**4**: To a solution of β-**11** (0.260 g, 0.571 mmol) in xylene (29 mL) was added $HgBr_2$ (0.103 g, 0.285 mmol). The mixture was refluxed for 2 h, and filtered through a pad of Celite. The filtrate was washed with water and dried over Na_2SO_4. The residue was purified by column chromatography

(30–40% EtOAc–hexane) to give α-**11** (0.128 g, 0.281 mmol, 49% yield) as a colorless foam. To a solution of α-**11** (46 mg, 0.10 mmol) in MeOH (1.0 mL) was added sodium methoxide (1.1 mg, 20 μmol). The mixture was stirred for 15 min at room temperature. After the mixture was evaporated, the residue was purified by silica-gel column chromatography (15% MeOH–$CHCl_3$) to give α-**4** (27 mg, 95% yield): colorless needles (MeOH–Et_2O): mp 128–132 °C; $[\alpha]_D^{25}$ +92.0 (*c* 0.50, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ: 3.43 (dd, *J* = 6.4 Hz, 6.0 Hz, 1H), 3.62 (dd, *J* = 6.4 Hz, 2.4 Hz, 1H), 3.64–3.69 (m, 2H), 3.74 (ddd, *J* = 6.8 Hz, 2.8 Hz, 2.0 Hz, 1H), 3.93 (t, *J* = 6.4 Hz, 1H), 6.46 (d, *J* = 2.4 Hz, 1H), 6.99 (dd, *J* = 5.2 Hz, 3.2 Hz, 1H), 7.31 (dd, *J* = 5.2 Hz, 0.8 Hz, 1H), 7.68 (dd, *J* = 3.2 Hz, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ: 56.4 (q), 62.4 (t), 71.4 (d), 73.1(d), 75.0 (d), 75.2 (d), 95.3 (d), 119.8 (d), 120.7 (d), 137.9 (d), 146.5 (s), 154.0 (s); IR (KBr): 3392, 3273, 2941, 1602, 1581, 1471, 1440, 1288, 1211, 999 cm^{-1}; MS (FAB) *m*/*z*: 288 ($[M+H]^+$), 126 (100%); HRMS (FAB) calcd for $C_{12}H_{18}NO_7$ ($[M+H]^+$): 288.1083, found: 288.1080.

7. Representative procedure of the β-glycosylation: 1-*O*-*cis*-cinnamoyl-β-D-glucopyranose (**1**): A suspension of α-**4** (10.0 mg, 34.8 μmol) in toluene (10 mL) was treated with *cis*-cinnamic acid (**2**) (0.516 g, 3.48 mmol) and the reaction mixture was stirred for 8 h at 70 °C. At this temperature, the mixture was gradually clear. After the mixture was evaporated, the residue was purified by silica-gel column chromatography (5–10% MeOH–$CHCl_3$) to remove the excess carboxylic acid, followed by HPLC (Mightysil Si 60, 10 × 250 mm, 5% MeOH–$CHCl_3$, flow rate 5.0 mL/min) to give **1** (9.8 mg, 32 μmol, 91% yield, α:β = 1:15) as a colorless oil. $[\alpha]_D^{25}$ +20.00 (*c* 0.10, MeOH); ^{1}H NMR (600 MHz, CD_3OD) δ: 3.32–3.44 (m, 4H), 3.68 (dd, *J* = 12.0 Hz, 5.4 Hz, 1H), 3.84 (dd, *J* = 12.0 Hz, 2.4 Hz, 1H), 5.54 (d, *J* = 7.8 Hz, 1H), 6.02 (d, *J* = 12.6 Hz, 1H), 7.09 (d, *J* = 12.6 Hz, 1H), 7.33–7.36 (m, 3H), 7.67–7.68 (m, 2H); ^{13}C NMR (150 MHz, CD_3OD) δ: 62.3 (t), 71.1 (d), 73.9 (d), 78.1 (d), 78.9 (d), 95.7 (d), 119.4 (d), 129.1 (d), 130.4 (d), 131.3 (d), 135.9 (s), 146.4 (d), 166.1 (s); IR (KBr): 3379, 2928, 1735, 1626, 1166, 1070 cm^{-1}; MS (ESI) *m*/*z*: 333 ($[M+Na]^+$), 333 (100%).