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Simple synthesis of phenylpropenoid β-D-glucopyranoside congeners based on Mizoroki–Heck type reaction of organoboron reagents

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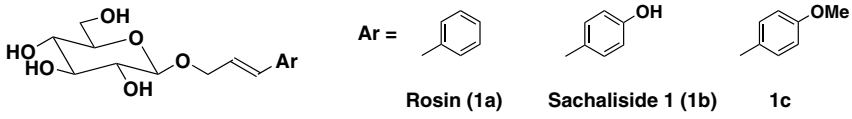
Abstract—Palladium(II)-catalyzed carbon–carbon bond formation between allyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**3**) and phenylboronic acid congeners gave the phenylpropenoid 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**4a–f**) in good yield. Among them, compounds **4a–c** were converted to the naturally occurring phenylpropenoid β-D-glucopyranoside analogues (**1a–c**).

1. Introduction

Golden root (Roseroot, *Rhodiola rosea* L., Crassulaceae) has been used for a long time as a resource in Chinese traditional medicine.[1] Phenylpropenoid glucoside, such as rosin (cinnamyl *O*-β-D-glucopyranoside; **1a**), was isolated from *R. rosea* as one of the major active ingredients and reported to be pharmacologically active as antioxidants and neurostimulants.[2] Moreover, some other phenylpropenoid glucoside analogues have been isolated as bioactive substances. For instance, sachaliside **1** (4-hydroxycinnamyl *O*-β-D-glucopyranoside; **1b**) and 4-methoxy-cinnamyl *O*-β-D-glucopyranoside (**1c**) have been isolated from the callus cultures of the plant (Scheme 1).[3]

To investigate their pharmacological activities, we have recently reported that the coupling of cinnamyl alcohol derivatives and 4-nitrophenyl β-D-glucopyranoside using β-glucosidase (EC 3.2.1.21) in phosphate buffer (pH 5) gave rosin (**1a**) and 4-methoxy-cinnamyl *O*-β-D-glucopyranoside (**1c**).[4] This process was useful for the synthesis of a variety of β-D-glucopyranoside analogues because a metal catalyst and protection of the hydroxyl groups on the glucose unit were not needed. However, in the case of the enzymatic glucosidation using hydrophobic alcohol, such as 4-methoxy-cinnamyl alcohol, excess amount of alcohol was needed (4 equiv) and chemical yield was poor (11%).[4b] Moreover, for the purpose of the diverse phenylpropenoid glucoside analogues using existing glucosidation methods, many kinds of the substituted cinnamyl alcohols should be synthesized. Now, we report a simple total synthesis of rosin (**1a**), sachaliside **1** (**1b**) and 4-methoxy-cinnamyl-*O*-β-D-glucopyranoside (**1c**) using the Mizoroki–Heck (MH) type reaction between the substituted arylboronic acid and allyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**3**) under Pd(II) condition as the key reaction (Scheme 2, step (iii)). The MH type reaction of phenylboronic acid and olefin under Pd(0)-catalyzed condition was shown by Cho and Uemura.[5a] On the other hand, organoboron-mediated MH type reaction via a Pd(II)-catalyzed



Scheme 1.

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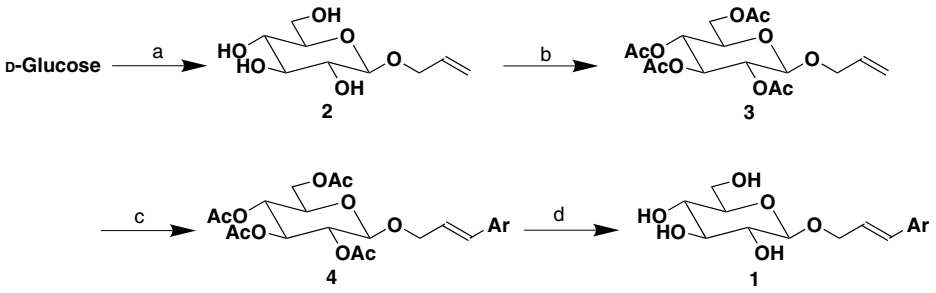


Scheme 2. Reagents and conditions: (a) ally alcohol/H_2O/immobilized β-glucosidase with ENTP-4000, 50 °C, 72 h, 60%; (b) Ac_2O/cat. DMAP/pyridine, rt overnight, 95%; (c) $ArB(OH)_2$/cat. $Pd(OAc)_2/Cu(OAc)_2$/LiOAc/DMF, 60–100 °C, 1–2 h, 45–75%; (d) K_2CO_3/MeOH, rt 1 h or NaOMe/MeOH, rt 1 h, 63–99%.

condition had been also reported by Du et al.[5b] However, the reaction of allyl ether with phenyl boronic acid was examined only one example in this literature[5b] and no other examples have been reported in the field of carbohydrate chemistry. Furthermore, we synthesized non-natural phenylpropenoid analogues to investigate the limitation of this strategy.

2. Synthesis of substrate for MH type reaction

Some synthesis of allyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**3**)[6] and the direct glucosidation of D-glucose using β-glucosidase (EC 3.2.1.21) from almonds have been reported.[7] Meanwhile, we had reported direct β-glucosidation between D-glucose and primary alcohol using the immobilized β-glucosidase (EC 3.2.1.21) from almonds with the synthetic prepolymer ENTP-4000 giving mono-β-D-glucopyranoside in moderate yield.[8] As in the previous method, allyl β-D-glucopyranoside (**2**) could be prepared from D-glucose and allyl alcohol using the immobilized β-glucosidase in 60% yield. Acetylation of allyl β-D-glucopyranoside (**2**) with acetic acid anhydride in pyridine afforded allyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**3**) as a key substrate for MH type reaction.

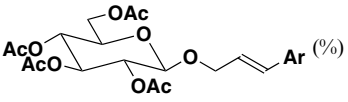
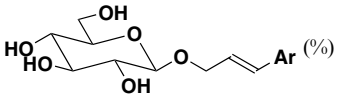
3. Results

The reaction of phenylboronic acid with allyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**3**) was carried out using LiOAc, $Cu(OAc)_2$, a catalytic amount of $Pd(OAc)_2$ in DMF at 100 °C for 1.5 h to give cinnamyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**4a**) in 71% yield (entry 1). As summarized in Table 1, phenylboronic acid having an electron-donating group (entry 3), an electron-withdrawing group (entries 4–6) and a non-protected hydroxyl group (entry 2) underwent MH type reactions smoothly in reasonable yield. After deprotection of coupling products (**4a–f**) using NaOMe/MeOH or K_2CO_3/MeOH, the desired phenylpropenoid β-D-glucoside analogues (**1a–f**)[9] were obtained rapidly. The spectroscopic data (^1H and ^{13}C NMR) and specific rotation {$[\alpha]_D$} of synthetic natural-type phenylpropenoid β-D-glucoside analogues (**1a–c**) were fully identical with those of natural products.

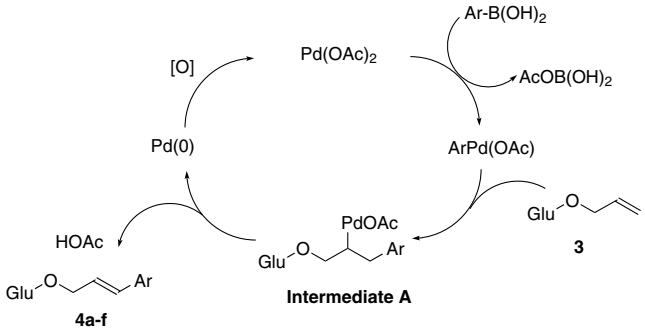
4. Discussion

The MH type reaction of silanols and organotin compounds with olefins via a Pd(II)-mediated pathway has been reported by Hiyama and co-workers.[10] Based on this pathway, a plausible MH type reaction mechanism with arylboronic acid was presented in Scheme 3. According to this mechanism, the aryl unit migrated to the palladium centre from arylboronic acid to furnish an aryl palladium species first, and this reactive aryl palladium species was added to an olefin of allyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**3**) to afford an intermediate A. After reductive β-elimination of the intermediate A occurred, the desired product was obtained along with the release of palladium(0). Finally,

Table 1. Reaction of phenylboronic acid with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside[a] and deprotection

Entry	Ar–B(OH)$_2$	 (%)	Deprotection[c] **A**: K_2CO_3/MeOH; **B**: NaOMe/MeOH	 (%)
1	Ph–B(OH)$_2$	**4a**: Ar=Ph (71)	**A**	**1a**: Ar=Ph (95)
2	4-(OH)Ph–B(OH)$_2$[b]	**4b**: Ar=4-(OH)Ph (57)	**B**	**1b:** Ar=4-(OH)Ph (95)
3	4-(OMe)Ph–B(OH)$_2$	**4c**: Ar=4-(OMe)Ph (72)	**A**	**1c**: Ar=4-(OMe)Ph (69)
4	4-Cl–Ph–B(OH)$_2$	**4d**: Ar=4-Cl–Ph (75)	**B**	**1d**: Ar=4-CI–Ph (85)
5	4-(CN)Ph–B(OH)$_2$	**4e**: Ar=4-(CN)Ph (75)	**B**	**1e**: Ar=4-(CN)Ph (99)
6	4-(CF_3)Ph–B(OH)$_2$	**4f**: Ar=4-(CF_3)Ph (45)	**A**	**1f**: Ar=4-(CF_3)Ph (63)

[a] Unless otherwise noted, all coupling reactions were carried out in DMF (4 mL), using 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (1.0 mmol), Ar–B(OH)$_2$ (1.2 mmol), $Pd(OAc)_2$ (0.1 mmol), $Cu(OAc)_2$ (2 mmol) and LiOAc (3 mmol) at 100 °C for 1.5 h.
[b] The amount of 4-hydroxyphenylboronic acid used was 3.0 mmol.
[c] Method **A**: K_2CO_3 (1.0 equiv based on **4a–f)** in MeOH, method **B**: 25% NaOMe in MeOH (1.0 equiv based on **4a–f)** in MeOH.



Scheme 3. The plausible MH type reaction mechanism with arylboronic acid.

the palladium(0) species was oxidized by a combination of copper(II) acetate and lithium acetate to regenerate palladium(II) as the key species of this catalytic reaction. Indeed, the treatment of allyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**3**) and phenylboronic acid in the presence of tetrakistriphenylphosphine palladium(0) affected removal of the allyl group instead of the desired MH type reaction. In addition, non-protected allyl β-D-glucopyranoside (**2**) could be reacted with arylboronic acid under the same conditions. However, the chemical yield was poor due to a low conversion. For instance, when allyl β-D-glucopyranoside (**2**) was treated with phenylboronic acid in the presence of LiOAc, $Cu(OAc)_2$, a catalytic amount of $Pd(OAc)_2$ in DMF at 100 °C for 5 h, the desired cinnamyl β-D-glucopyranoside (**1a**) could be obtained in only 11% along with a large amount of the starting material. This phenomenon might be explained by the deactivation of arylboronic acid due to the formation of arylboronic ester from arylboronic acid and allyl β-D-glucopyranoside (**2**). In fact, 4,4,5,5-tetramethyl-2-(4-hydroxyphenyl)-1,3-dioxaborane could not be reacted with allyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**3**) under the same conditions and it was suggested that a boronic ester was less reactive than a boronic acid to react with an allyl ether in this case.

5. Conclusion

In conclusion, a variety of natural and non-natural type phenylpropenoid glucopyranoside analogues have been synthesized based on the MH type reaction. Therefore, structurally diverse phenylpropenoid β-D-glucopyranoside analogues could be prepared using a number of commercially available substituted phenylboronic acids.

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