



Short synthesis of phenylpropanoid glycoside grayanoside-A and analogues



Duc Think Khong, Zaher M.A. Judeh*

School of Chemical and Biomedical Engineering, Nanyang Technological University, 62 Nanyang Drive, N1.2–B1-14, 637459, Singapore

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ABSTRACT

A short synthesis of phenylethyl glycosides grayanoside-A **1**, **2** and analogues **3–4** in high 43–65% overall yields is described. The main synthetic step involved regioselective O-6 acylation of unprotected 2-phenylethyl-β-D-glucoside **7** with cinnamoyl chlorides **8a–d** using Me₂SnCl₂ as catalyst. The acylation at O-6 is regioselective regardless of the type of cinnamoyl chloride used. Protection/deprotection steps of the glucoside core were not necessary. The synthetic route is generally applicable for the synthesis of phenylpropanoid glycoside class of compounds acylated at O-6.

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1. Introduction

Phenylpropanoid glycosides (PhGs) are natural compounds distributed in plants and show antioxidation, antiproliferation, antibacterial, antiviral, anti-inflammatory and hepatoprotection activities [1]. PhGs have 2-phenylethyl-β-D-glucoside core acylated with a (substituted) cinnamoyl moiety mainly at O-4 or O-6 and may have additional one or two saccharide units bonded to the glucoside core through glycosidic bonds (Fig. 1).

Total synthesis of PhGs has attracted significant interests due to their diverse bioactivities. The conventional approach for their synthesis has mainly relied on tedious, low-yielding and multistep protection-deprotection strategies [2]. Our group has been interested in developing short and convenient synthesis of PhGs that eliminate unnecessary protection/deprotection steps. To this end, we focused our attention at synthesizing PhG class of compounds acylated at O-6 since they represent the vast majority of the reported PhGs. We recently communicated the synthesis of calceolarioside-B and eutigioside-A [3]. It was natural for us to extend our synthetic efforts to grayanoside-A **1**, [4] PhG **2** [5] (no name was given to this reported PhG) and test the general applicability of the approach by synthesizing PhGs analogues **3–4** having cinnamoyl moieties at O-6 (Fig. 1). The reported synthesis of grayanoside-A **1** involved acylation of the glucoside core at O-6 with feruloyl acid chloride in pyridine [2g] or protection-

deprotection strategies [2a]. The use of feruloyl, coumaroyl and cinnamoyl acid chlorides/pyridine system for selective acylation of primary hydroxyl groups of sucrose has been employed in our lab for the synthesis of various phenylpropanoid sucrose esters [6]. It usually resulted in unpredictable mixtures of acylated products that were tedious to purify. Therefore, a general selective and more predictable approach is needed to prepare the phenylpropanoid glycoside class of compounds acylated at O-6.

Herein, we report a short synthetic route for grayanoside-A **1** and demonstrate its general applicability for the synthesis of O-6 acylated PhGs analogues **2–4**. This route relies on direct O-6 acylation of unprotected glucoside core in high selectivity and yield without protection/deprotection steps. The route is general for the synthesis of phenylpropanoid glycosides class of compounds acylated at O-6.

2. Results and discussion

Our synthesis of grayanoside-A **1**, PhG **2** and analogues **3–4** is depicted in Scheme 1. Direct 1,2-*trans*-β-glycosylation between excess peracetate D-glucose **5** and 2-(4-allyloxyphenyl)ethanol **6** followed by deacetylation using NaOMe/MeOH gave 2-(4-allyloxyphenyl)ethyl-β-D-glucopyranoside **7** in 82% yield [3]. We noted that the use of excess rather than stoichiometric amount of peracetate D-glucose **5** was beneficial as it gave higher yield of glucopyranoside **7** [2a]. The glycosylation reaction proceeded through neighboring group participation mechanism [7].

Next, direct regioselective O-6 acylation of 2-(4-allyloxyphenyl)

* Corresponding author.

E-mail address: zaher@ntu.edu.sg (Z.M.A. Judeh).

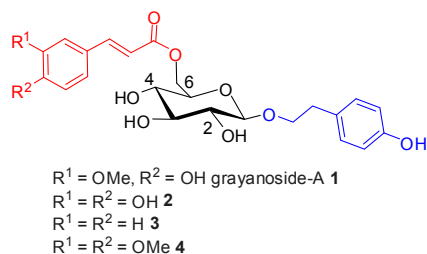


Fig. 1. Structures of grayanoside-A **1**, PhG **2** and analogues **3–4**.

ethyl- β -D-glucopyranoside **7** with acid chlorides **8a–d** [8] using catalytic amount of Me_2SnCl_2 [9] gave the desired *O*-6 acylated glucosides **9a–d** in 79–86% yield (Scheme 1). The preferential acylation of cinnamoyl chloride at *O*-6 is due to the higher intrinsic reactivity of 6-OH [10] and the increased acidity of 6-OH after complexation with Me_2SnCl_2 [9].

Finally, removal of the allyl groups of the acylated glucosides **9a, c–d** using Pd/C proceeded smoothly to give grayanoside-A **1** in 74% yield and analogues **3** and **4** in 92% and 89% yields, respectively. Removal of the *tert*-butyldimethylsilyl (TBS) groups of acylated glucoside **9b** using tetra-*n*-butylammonium fluoride (TBAF) followed by removal of the allyl group using Pd/C gave PhG **2** in 67% yield. In all cases, no migration and/or hydrolysis [2g,h] of the cinnamoyl moieties occurred as the allyl and TBS groups were removed selectively. The structures of grayanoside-A **1** and PhG **2** were confirmed by ^1H NMR and ^{13}C NMR and matched with the reported data [2a,g,5].

3. Conclusion

We have developed a short synthesis of grayanoside-A **1** and PhG **2** and analogues **3–4** in high 43–65% overall yields without protection-deprotection steps. The first key step involved 1,2-*trans*- β -glycosylation of peracetylated D-glucose **5** with 2-(4-allyloxyphenyl)ethanol **6** to give 2-(4-allyloxyphenyl)ethyl- β -D-glucopyranoside **7**. The second key step involved regioselective *O*-6 acylation of unprotected 2-phenylethyl- β -D-glucoside **7** with cinnamoyl chlorides **8a–d** using Me_2SnCl_2 as catalyst. Acylation at *O*-6 is regioselective regardless of the type of cinnamoyl chloride used.

No migration and/or hydrolysis of the cinnamoyl moieties were observed at any stage. Because of convenience and high yields, this work serves as a model for the direct synthesis of phenylpropanoid glycoside class of compounds acylated at *O*-6.

4. Experimental

4.1. General procedures

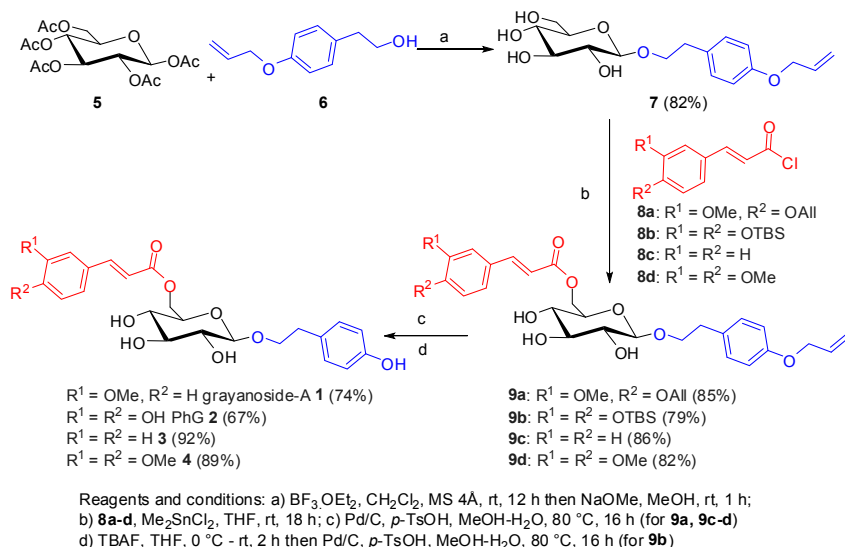
Chemical reagents were purchased from Sigma-Aldrich or Alfa Aesar and used as received without further purification. ^1H NMR spectra were recorded at 300 MHz on a Bruker Avance DPX 300. Unless stated otherwise, data refer to solutions in CDCl_3 with TMS as an internal reference. ^{13}C NMR spectra were recorded at 75.47 MHz on a Bruker Avance DPX 300. HRMS were recorded on Qstar XL MS/MS system. FTIR spectra were recorded on Perkin Elmer FTIR system Spectrum BX. Analytical TLC was performed using Merck 60 F₂₅₄ precoated silica gel plates (0.2 mm thickness) and visualized using UV radiation (254 nm). Flash chromatography was performed using Merck silica gel 60 (230–400 mesh).

4.2. General procedure for *O*-6 acylation of 2-(4-allyloxyphenyl)ethyl β -D-glucopyranoside **7** with cinnamoyl chloride **8a–d**

To a solution of glucopyranoside **7** (85 mg, 0.25 mmol) in THF (2.5 mL) was added Me_2SnCl_2 (2.75 mg, 5 mol%), cinnamoyl chloride **8** (0.375 mmol), DIPEA (87 μL , 0.5 mmol) under strong stirring. The reaction was stirred for ~18 h (TLC) before diluting with deionized H_2O (10 mL). The mixture was extracted with EtOAc (10 mL \times 3), the combined organic phases were washed with brine, dried over MgSO_4 , filtered and evaporated. The crude residue was purified by flash column chromatography to give the respective *O*-6 acylated products. The general method was used to prepare compounds **9a–d**.

4.2.1. 2-(4-Allyloxyphenyl)ethyl 6-*O*-(*E*)-(3-methoxy-4-allyloxy) cinnamoyl β -D-glucopyranoside **9a**

The crude product was purified by flash column chromatography (EtOAc: DCM = 3: 1) to give 120 mg (85% yield) as amorphous solid. $[\alpha]_D^{25} - 25^\circ$ (c 0.023, CH_2Cl_2). ^1H NMR (CDCl_3) δ : 2.80 (t, $J = 7.2$ Hz, 2H), 3.32–3.43 (m, 3H), 3.50–3.56 (m, 1H), 3.62 (q, $J = 8.4$ Hz, 1H), 3.79 (s, 3H), 4.00 (q, $J = 7.9$ Hz, 1H), 4.25 (d,



Scheme 1. Synthesis of grayanoside-A **1**, PhG **2** and analogues **3–4**.

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