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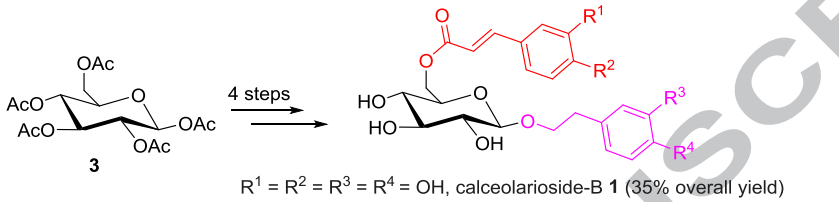

$R^1 = R^2 = R^3 = R^4 = OH$, calceolarioside-B **1** (35% overall yield)
$R^1 = H$, $R^2 = OH$, $R^3 = H$, $R^4 = OH$, eutigoside-A **2** (57% overall yield)

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Short synthesis of phenylpropanoid glycosides calceolarioside-B and eutigoside-A

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ABSTRACT

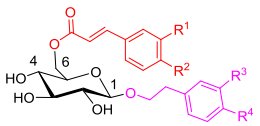
A convenient 4-step synthesis of calceolarioside-B **1** and eutigoside-A **2** in high overall yield is described. The key step involved the regioselective, Me_2SnCl_2-catalyzed *O*-6 acylation of unprotected 2-phenylethyl-β-D-glucosides **5a-b** with cinnamoyl chlorides **6a-b** in excellent yields. Acylation at *O*-6 is selective with the acid chlorides used. This work serves as a model for the convenient synthesis of phenylpropanoid glycosides acylated at *O*-6.

1. Introduction

Phenylpropanoid glycosides (PhGs) are secondary metabolites that are widely distributed in plants and show antioxidation, antiproliferation, antibacterial, antiviral, anti-inflammatory and hepatoprotection activities.[1,2] Simple PhGs contain a 2-phenylethyl-β-D-glucoside core unit acylated with a cinnamoyl moiety, mainly at *O*-4 or *O*-6 (Fig. 1) while more complex PhGs contain an additional one or two saccharide units bonded to the glucose core through glycosidic bonds.

The total synthesis of PhGs has attracted significant interest from medicinal and synthetic chemists to uncover their potential. However, their synthesis has mainly relied on tedious, low-yielding and multistep protection-deprotection strategies in order to assemble the cinnamoyl moiety at the correct position on the glucose core.[3-11] These strategies are further complicated by the incompatibilities between the cinnamoyl and the protecting groups under the conditions for protection/deprotection. For example, when benzyl ether protecting groups were removed by hydrogenolysis, reduction of the cinnamoyl moieties olenfinic bonds occurred.[3,5,11] Likewise, removal of the acetyl and chloroacetyl protecting groups resulted in hydrolysis and/or migration of the cinnamoyl moieties.[9,10] Recently, Mong and co-workers [8] successfully reported an orthogonal multistep synthesis of calceolarioside-B **1** and other PhGs. The synthesis relied on a protection/deprotection methodology using naphthylidene acetal, naphthylmethyl and allyl ether protecting groups that were selectively removed.

Calceolarioside-B **1**[12] and eutigoside-A **2**[13,14] (Fig. 1) possess potential antiproliferation activities against various tumor cell lines including prostatic cancer cells,[8] human bladder carcinoma T-24 cells,[14] human gastric adenocarcinoma,[15] human uterus carcinoma,[15] and murine melanoma.[15] Despite their structural simplicity, their syntheses have been reported using multistep procedures with extensive and cumbersome protection/deprotection steps.[3, 8]



$R^1 = R^2 = R^3 = R^4 = OH$, calceolarioside-B **1**
$R^1 = H$, $R^2 = OH$, $R^3 = H$, $R^4 = OH$, eutigoside-A **2**

Figure 1. Structures of calceolarioside-B **1** and eutigoside-A **2**

Herein, we report a convenient, high-yielding synthesis of calceolarioside-B **1** and eutigoside-A **2** without protection/deprotection steps. The synthetic strategy relies on a regioselective Me_2SnCl_2-catalyzed *O*-6 acylation of an unprotected glucose core. The strategy is applicable to the synthesis of phenylpropanoid glycosides acylated at *O*-6.

2. Results and Discussion

Our proposed synthetic route for calceolarioside-B **1** and eutigoside-A **2** entails two main steps as outlined in Scheme 1. The first step involves 1,2-*tran*-β-glycosylation of peracetylated D-glucose **3** with 2-phenylethanols **4** through a neighboring group participation mechanism to give 2-phenylethyl-β-D-glucoside **5**. The second key step involves the regioselective *O*-6 acylation of

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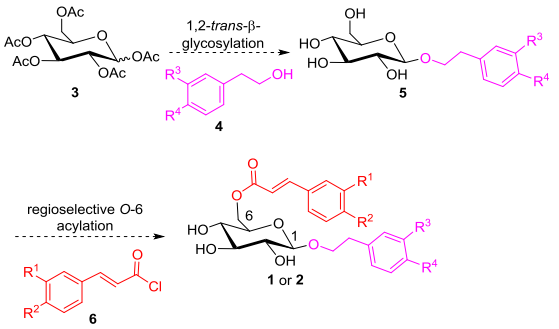
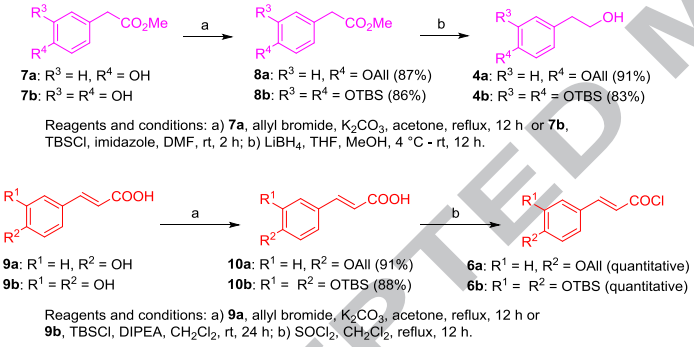
the unprotected 2-phenylethyl-β-D-glucoside **5** with cinnamoyl chlorides **6**.



Scheme 1. Proposed synthetic route for calceolarioside-B **1** and eutigoside-A **2**

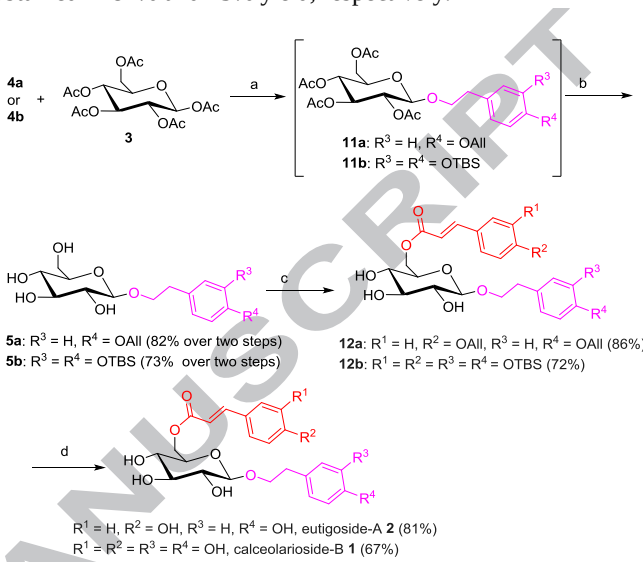
2-Phenylethanols **4** were prepared in two steps (Scheme 2). Protection of the hydroxyl group of 4-hydroxyphenyl acetate ester **7a** with allyl bromide gave the *O*-allyl ester **8a** in 87% yield.[16] Protection of the hydroxyl groups of 3,4-dihydroxyphenyl acetate ester **7b** with *tert*-butyldimethylsilyl chloride (TBSCl) gave the *O*,*O*-diTBS ester **8b** in 86% yield.[4] Ester **7b** was protected with TBSCl rather than allyl bromide because we found that treatment of *O*,*O*-diallyl esters with Pd/C always led to incomplete deprotection. Reduction of esters **8a-b** to the corresponding 2-phenylethanols **4a-b** was achieved using $LiBH_4$[17] in 91% and 83% yield, respectively.[4, 9]



Scheme 2. Synthesis of 2-phenylethanols **4a-b** and cinnamoyl chlorides **6a-b**

Cinnamoyl chlorides **6** were also prepared in two steps (Scheme 2). The hydroxyl group of coumaric acid **9a** was protected using allyl bromide to give *O*-allyl coumaric acid **10a** in 91% yield.[18] The hydroxyl groups of caffeic acid **9b** were protected using TBSCl to give *O*,*O*-diTBS cafeic acid **10b** in 88% yield (Scheme 2).[19] Conversion of acids **10a-b** to their acid chlorides **6a-b** was readily achieved in quantitative yield by heating at reflux with $SOCl_2$ in CH_2Cl_2.[20,21] These acid chlorides were recrystallized from anhydrous toluene prior to acylation with 2-phenylethyl-β-D-glucoside **5a-b**.

Having synthesized the required 2-phenylethanols **4a-b** and cinnamoyl chlorides **6a-b**, we then proceeded with the synthesis of calceolarioside-B **1** and eutigoside-A **2** according to our proposed route (Scheme 1). To obtain glucoside **5**, 1,2-*trans*-β-glycosylation is traditionally performed between 2-phenylethanols and protected D-glucose containing bromide, chloride and trichloroacetimidate leaving groups at C1.[11] In this work, direct glycosylation between 2-phenylethanols **4a-b** and excess peracetate D-glucose **3** using $BF_3{\cdot}OEt_2$ gave the corresponding glucosides **11a-b**.[3] Although excess peracetate D-glucose **3** provided the desired glucosides in higher yields compared to stoichiometric amounts, this complicated the purification process. Because we were unable to separate pure glucosides **11a-b**, their crude glycosylation reaction mixtures were subjected to deacetylation using NaOMe/MeOH. After complete deacetylation and purification using column chromatography, pure 2-phenylethyl-β-D-glucosides **5a-b** were obtained in 82% and 73% yield, respectively.



Scheme 3. Synthesis of calceolarioside-B **1** and eutigoside-A **2**

Next, we examined the direct regioselective *O*-6 acylation of 2-phenylethyl-β-D-glucosides **5a-b** with cinnamoyl chlorides **6a-b** using various Lewis acids including Me_2SnCl_2,[22] $Sn(OTf)_2$,[23] $Cu(OTf)_2$,[23] $Yb(OTf)_3$[24] and $Sc(OTf)_3$.[25,26] We also attempted the acylation reaction under basic conditions using pyridine.[9,27,28] The reactions gave 67%-94% yields of mixtures containing multiple acylation products (mainly *O*-4 and *O*-6 mixtures). However, after optimization, Me_2SnCl_2[22] gave the desired *O*-6 acylated glucosides **12a-b** in 86% and 72% yield, respectively (Scheme 3). Direct acylation without catalysts is dependent on the type of cinnamoyl chloride and reaction conditions.[9, 27, 28]

Finally, deprotection of the allyl groups of glucoside **12a** using Pd/C gave eutigoside-A **2** in 81% yield while deprotection of the TBS groups of glucoside **12b** using tetra-*n*-butylammonium fluoride (TBAF) gave calceolarioside-B **1** in 67% yield. The structures of both calceolarioside-B **1** and eutigoside-A **2** were confirmed by ^{1}H NMR and ^{13}C NMR and matched with the reported data.[8, 14]

3. Conclusion

We have developed a short 4-step synthesis of calceolarioside-B **1** and eutigoside-A **2** that avoids troublesome protection/deprotection approaches and their incompatibilities with the cinnamoyl moieties. Both calceolarioside-B **1** and eutigoside-A **2** were obtained, respectively, in excellent 35% and 57% overall yields. The key step in this synthesis involved the regioselective Me_2SnCl_2-catalyzed *O*-6 acylation of unprotected 2-phenylethyl-β-D-glucosides **5a-b** with cinnamoyl chlorides **6a-b**. In our approach, acylation at *O*-6 is selective with the acid chlorides used. Because of convenience and high yields, this work is envisioned to serve as a model for the direct synthesis of PhGs acylated at *O*-6.

Acknowledgment

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Supplementary data

Supplementary data (experimental procedures, ^{1}H NMR and ^{13}C NMR spectra of synthesized compounds) associated with this article can be found, in the online version, at…

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Highlights:

- Short synthesis of calceolarioside-B and eutigoside-A
- General route applicable to the synthesis of PhGs acylated at *O*-6
- Acylation at *O*-6 is selective
- No protection/deprotection steps