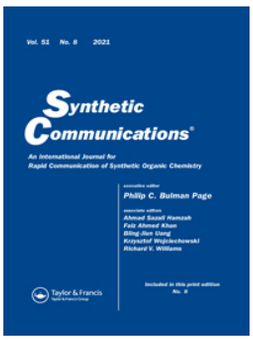

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First total syntheses of four natural bioactive glucosides

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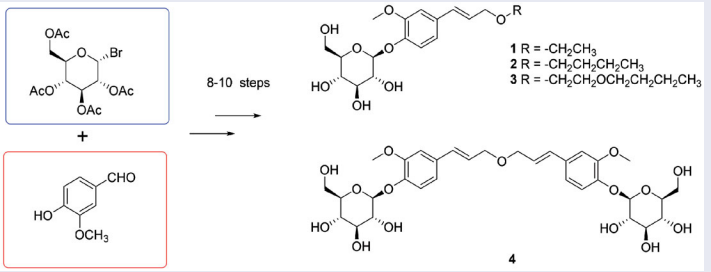
ABSTRACT

The efficient total syntheses of four biologically interesting natural glucosides Ethylconiferin, Butylconiferin, 2′-Butoxyethylconiferin and Balajaponin B, have been achieved for the first time starting from commercially available Vanilline via concise reaction sequence of 8–10 steps with the overall yield of 26–41%. This work definitely laid the foundation for the further pharmacological study of this kind of natural compounds. Meanwhile, currently developed approach could be used as a general synthetic strategy for the syntheses of other monolignol glucosides and their derivatives, and provides an opportunity for further study of the structure-activity relationship of this kind of glucosides.

GRAPHICAL ABSTRACT



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KEYWORDS
Balajaponin B; 2′-Butoxyethylconiferin; butylconiferin; Ethylconiferin; total synthesis

Introduction

Monolignol glucosides (Coniferin, *p*-Glucocoumaryl alcohol, Syringin, Fig. 1) are considered to be the storage or excretion form of monolignols which are widely distributed plant metabolites associated with wide range of biological activities.[1–5] Over the past several decades, significant research attention has been directed to the investigation of these compounds. Recently, various bioactivities and pharmaceutical activities of Coniferin have been reported, including antioxidative activity,[6] antinociceptive

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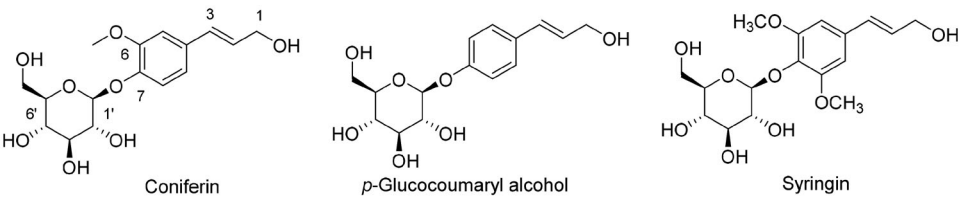


Figure 1. Structures of some typical monolignol glucosides.

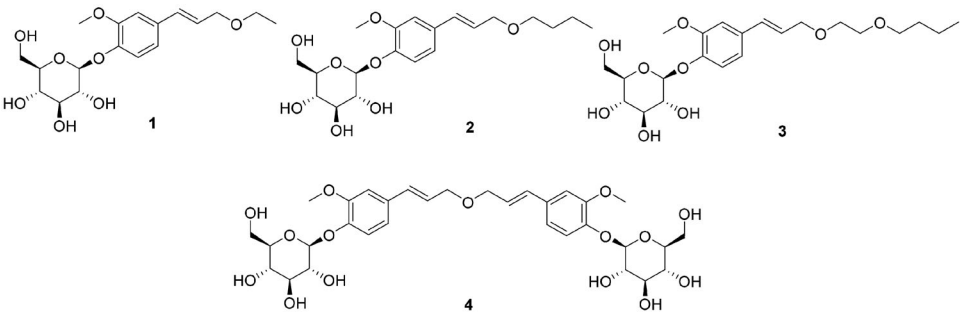


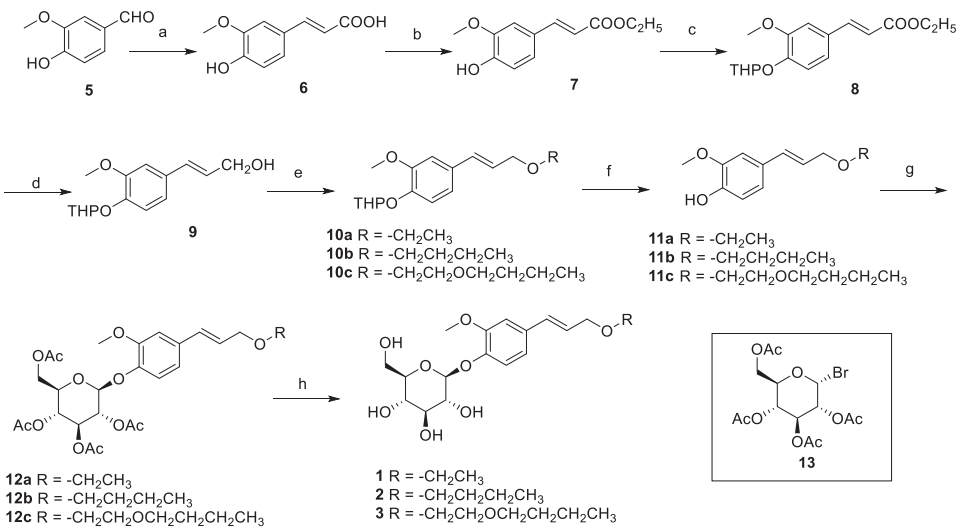
Figure 2. Structures of Ethylconiferin (**1**), Butylconiferin (**2**), 2′-Butoxyethylconiferin (**3**) and Balajaponin B (**4**).

activity,[7] anti-inflammatory activity,[8] α-Glucosidase inhibitory activity and antihyperglycemic activity.[9]

As shown in Figure 2, Ethylconiferin (**1**), Butylconiferin (**2**), 2′-Butoxyethylconiferin (**3**) and Balajaponin B (**4**) could be considered to be the structural relatives of Coniferin and also exhibited diverse biological activities. Ethylconiferin (**1**) was first isolated from the root of *Jasminum* giraldii Diels (Oleaceae).[10] Butylconiferin (**2**) was isolated from a Chinese traditional herbal drugs *Balanophora simaoensis* [11]as well as the branches of *Lawsonia inermis* L.[12]and showed accelerative effects on neurite outgrowth in PC12 cells.[13] 2′-Butoxyethylconiferin (**3**) was one of main anti-inflammatory constituents of annual herbaceous plant *Bidens frondosa* (L.)[14] Balajaponin B (**4**) was obtained from *Balanophora japonica* Makino (Balanophoraceae) and showed *in vitro* glucosidase inhibitory activity.[15] To date, these compounds have attracted scientific attention as the result of their diverse biological activities. However, the low content of them has limited the further investigation of these activities. Although the total syntheses of Coniferin have been reported for several times,[16,17] an appropriate synthetic methodology to obtain natural products **1–4** and diverse analogues of Coniferin is still required. Herein we reported the first total syntheses of Ethylconiferin (**1**), Butylconiferin (**2**), 2′-Butoxyethylconiferin (**3**) and Balajaponin B (**4**).

Results and discussion

The syntheses of natural products **1–3** shown in Scheme 1 began with readily available Vanillin (**5**). We started with the conversion of **5** to Ferulic acid (**6**) by the Knoevenagel condensation in 94% yield. Compound **6** was refluxed in absolute alcohol in the presence of concentrated H_2SO_4 to get ester **7**, in which the phenolic hydroxyl group was

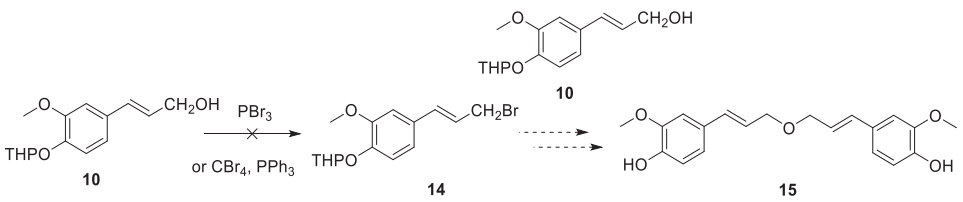


Scheme 1. Reagents and conditions: (a) $CH_2(COOH)_2$, piperidine, *p*-methylaniline, $PhCH_3$, 80 °C, 94%; (b) H_2SO_4, CH_3CH_2OH, reflux, 94%; (c) Dihydropyran, PPTS, 65 °C, 75%; (d) BnCl, $LiAlH_4$, THF, r.t., 90%; (e) NaH, DMF, r.t., **10a**:CH_3CH_2I, 93%, **10 b**: $CH_3CH_2CH_2CH_2I$, 90%, **10c**: $CH_3CH_2OCH_3CH_2CH_2CH_2Cl$, 78%; (f) PPTS, CH_3OH, r.t.; (g) Compound **13**, TBAB, K_2CO_3, $H_2O/CHCl_3$, 65 °C, **12a**: 77%, **12 b**: 73%, **12c**: 82% for two steps; (h) CH_3ONa, CH_3OH, **1**: 95%, **2**: 97%, **3**: 96%.

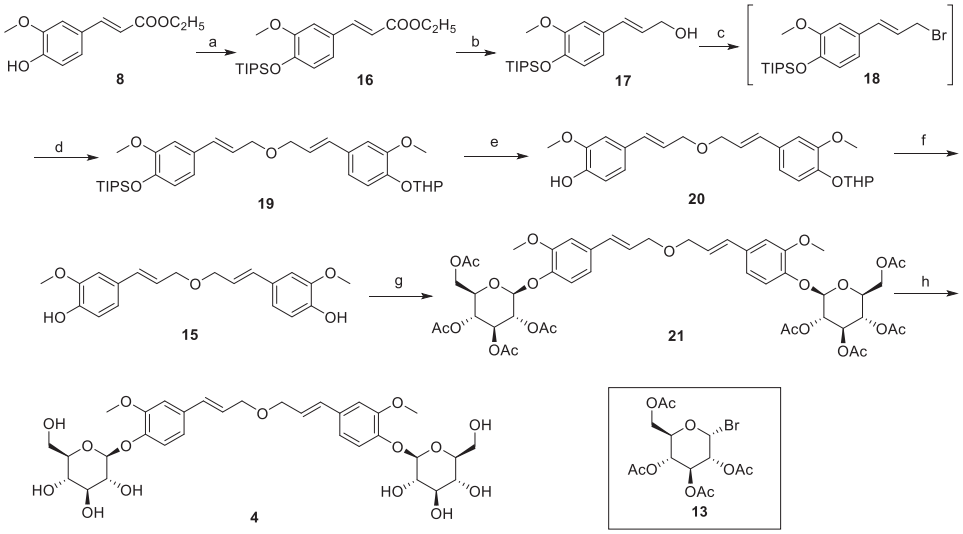
protected as tetrahydropyranyl ether (−OTHP) to obtain cinnamate **8**. Subsequently the ester group of **8** was reduced by $LiAlH_4$ to obtain key intermediate **9**. Then ethers **10a-c** were formed by coupling corresponding alkyl halides to compounds **9** in the presence of NaH, respectively. Deprotection of the THP groups of compounds **10a-c** with PPTS in CH_3OH resulted in formation of compounds **11a**, **11 b** and **11c** smoothly. Glycosylation of aglycones **11a-c** with 2,3,4,6-tetra-*O*-acetyl-α-$_D$-glucopyranosyl bromide (**13**) under basic conditions, in the presence of the phase transfer catalyst tetra-butylammonium bromide (TBAB), afforded compound **12a-c** in good yields (77%–82%).[18] The target natural products **1–3** were obtained from **12a-c** by direct deacetylation with CH_3ONa/CH_3OH in excellent yields (over 95% to almost in quantitative).

As shown in Scheme 2, our strategy for the total synthesis of Balajaponin B (**4**) involved a key intermediate aglycone **15**. Initially we wanted to convert cinnamyl alcohol **10** to cinnamyl bromide **14**, which could be coupled with **10** to afford aglycone **15**. However, the attempts to obtain **14** via Appel-Lee reaction (in the presence of CBr_4 and PPh_3) or PBr_3 brominated reaction were unsuccessful due to the high instability of **14**.

As shown in Scheme 3, the synthetic route was then modified. In the modified route, phenolic hydroxyl group of **8** was protected by triisopropylsilyl ether (-OTIPS), which was more stable than tetrahydropyranyl ether (-OTHP) under brominated conditions to get cinnamic acid ethyl ester **16**. Compound **16** was reduced, brominated and coupled with compound **10** to form protected aglycone **19** successfully. The TIPS group of **19** was removed by treatment with tetra-*n*-butylammonium fluoride (TBAF) followed by deprotection in the presence of PPTS\CH_3OH to afford aglycone **15**. Glycosylation of compound **15** with 3 equiv. of 2,3,4,6-tetra-*O*-acetyl-α-$_D$-glucopyranosyl bromide (**13**) under similar conditions above, yielded compound **21** in 60%. Compound **21** was



Scheme 2. Desigh of initial attempt to prepare **15**.



Scheme 3. Reagents and conditions: (a) TIPSCl, imidazole, DMF, r.t., 93%; (b) BnCl, $LiAlH_4$, THF, r.t., 77%; (c) PBr_3, THF, 0 °C; (d) Compound **10**, NaH, DMF, r.t. to −20 °C, 66% for 2 steps; (e) TBAF, THF, 0 °C, 97%; (f) PPTS, CH_3OH, 99%; (g) Compound **13**, TBAB, K_2CO_3, $H_2O/CHCl_3$, 65 °C, 60%; (h) CH_3ONa, CH_3OH, 85%.

treated subsequently with CH_3ONa in CH_3OH to generate the desired natural products **4** in 85% yield.

Based on the above synthetic routes, the key steps of the present processes are TBAB promoted glycosylations between aglycones (**11a-c**, **15**) with 2,3,4,6-tetra-*O*-acetyl-α-$_D$-glucopyranosyl bromide (**13**) in CH_2Cl_2-water solvent system. The glycosylations led to the desired *β*-*O*-glucosides in good yields (60%–82%) and the coupling constant of $H_{1'}$-$H_{2'}$ of compound **1–3** and **4** indicated high stereoselective formation of beta-glycosidic bond ($^3J_{1'2'} = 7.2–7.4$ Hz in the ^{1}H NMR spectra).

Conclusions

In summary, the first total syntheses of the naturally occurring and biologically interesting Ethylconiferin (**1**), Butylconiferin (**2**), 2′-Butoxyethylconiferin (**3**) and Balajaponin B (**4**) via a same strategy have been achieved. Syntheses of **1–3** utilized eight-step syntheses from the commercially available Vanillin (**5**) and gave compound **1–3** in overall yields of 37%–41%. However, 10 steps were required to produce **4** in an overall yield of

26% from the same starting material. The total syntheses of these compounds thus provides an efficient synthetic route to diverse coniferin derivatives that can be used in further investigations.

Experimental

Synthesis of ethylconiferin (1)

Under N_2 atmosphere, the acetyl-protected glycoside **12a** (0.43 g, 0.8 mmol) was dissolved in 60 ml of CH_3OH. After that, CH_3ONa (130 mg, 2.4 mmol) was added. Then the mixture stirred at room temperature for 1 h. When the deprotection was completed, the solution was neutralized by ion-exchange resin (Amberlite IR120). The agitation was maintained for 10 min, and then filtered. The CH_3OH was eliminated by vacuum evaporation to afford compounds **1** (0.28 g, 95%) as a white solid: $[\alpha]_D$ −19.5 (CH_3OH, c = 0.11); ^1H NMR (CD_3OD) δ 7.08 (d, J = 8.3 Hz, 1H), 7.05 (d, J = 1.9 Hz, 1H), 6.93 (dd, J = 8.4, 1.9 Hz, 1H), 6.54 (d, J = 15.9 Hz, 1H), 6.21 (dt, J = 15.9, 6.2 Hz, 1H), 4.87 (d, J = 7.4 Hz, 1H), 4.09 (dd, J = 6.2, 1.4 Hz, 2H), 3.86 (m, 1H), 3.85 (s, 3H), 3.72–3.62 (m, 1H), 3.57–3.50 (m, 2H), 3.49–3.41 (m, 2H), 3.40–3.35 (m, 1H), 3.28 (dt, J = 3.2, 1.6 Hz, 1H), 1.19 (t, J = 7.0 Hz, 3H); ^{13}C NMR (CD_3OD) δ 149.5, 146.5, 132.0, 131.9, 124.6, 119.5, 116.5, 110.0, 101.4, 76.9, 76.5, 73.5, 70.9, 70.0, 65.3, 61.2, 55.4, 14.1; HRMS(ESI) calcd for $C_{18}H_{26}O_8Na$ $[M+Na]^+$ 393.1520, found 393.1515. The spectral and physical characteristic of the compound is agreement with that reported in the literature by Yue et al.[10]

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