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First total syntheses of two natural glycosides

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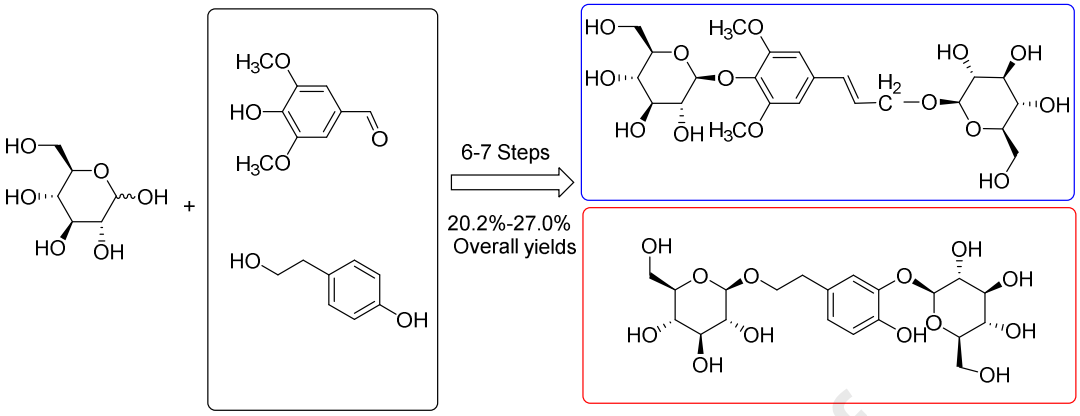
Graphical Abstrsct



Two natural bioactive glycosides, Isosyringinoside (**1**) and 3-(*O*-*β*-$_D$-glucopyranosyl)-α-(*O*-*β*-$_D$-glucopyranosyl)-4-hydroxy phenylethanol (**2**), were first totally synthesized via 6-7 steps with overall yields of 20.2% and 27.0%, respectively.

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Abstract

Isosyringinoside (**1**) and 3-(*O*-β-$_D$-glucopyranosyl)-α-(*O*-β-$_D$-glucopyranosyl)-4-hydroxy phenylethanol (**2**), the natural bioactive compounds contained unique structures, were first totally synthesized using easily available materials in short convenient routes with overall yields of 20.2% and 27.0%, respectively. An efficient total synthesis of **1** was developed in six steps, which contained two key steps of highly regioselective glycosylation without any selective protection steps. The seven-step synthesis of **2** involved two steps of regioselective glycosylations using BF_3-$O(C_2H_5)_2$ and TMSOTf as catalysts, respectively.

Key words

Total synthesis

Glycosides

Isosyringinoside

3-(*O*-β-$_D$-glucopyranosyl)-α-(*O*-β-$_D$-glucopyranosyl)-4-hydroxy phenylethanol

1. Introduction

The *O*-glycoside designates the structure with an aglycone moiety and sugar(s), which are directly connected through the C−O bond linkage. It is an important kind of organic compounds that exists widely in nature and encompasses a vast number of secondary metabolites. Members of *O*-glycosides embody various range of biological activities, especially antitumor, anti-infective and immunomodulatory effects [1]. The connection of bioactive aglycones to hydrophilic sugar rings could improve their pharmacokinetic properties and bioavailabilities in physiological fluids [2]. Depending on the different glycosidic bonds, the *O*-glycoside can be classified as phenolic glycoside and alcoholic glycoside, which show diverse pharmacokinetic and pharmacodynamic properties.

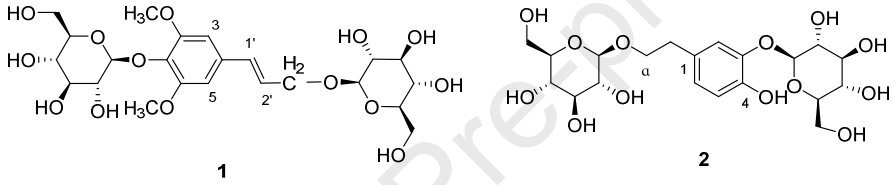


Figure 1. Structures of compounds **1** and **2**

As shown in Figure 1, natural products isosyringinoside (**1**) and 3-(*O*-*β*-$_D$-glucopyranosyl)-α-(*O*-*β*-$_D$-glucopyranosyl)-4-hydroxy phenylethanol (**2**) contained unique structures of both phenolic and alcoholic glycosides. Isosyringinoside (**1**) was first isolated in 1993 from bark of *Osmanthus asiaticus*, which was not only an ornamental plant growing in southwest China, but also a well-known traditional Chinese herbal medicine [3]. Isosyringinoside (**1**) has also been obtained from the fruit of *Lycium barbarum* L. (Solanaceae) (goji or wolfberry) [4] and other plants [5]. Due to its novel chemical structure, isosyringinoside (**1**) exhibited significant super oxide anion scavenging activity [5e] and triglyceride-lowering effect [5a]. 3-(*O*-*β*-$_D$-glucopyranosyl)-*α*-(*O*-*β*-$_D$-glucopyranosyl)-4-hydroxy phenylethanol (**2**) was first isolated from aerial parts of Teucrium polium L. by Elmasri and co-workers in 2014 [6]. It also has been obtained from the fruit parts of Chinese folk medicine Sambucus williamsii Hance [7], as well as Aconitum tanguticum (Maxim) Stapf (Ranunculaceae) [8]. In 2015, Wang and Li evaluated the anti-inflammatory activity of compound **2** by testing the inhibition of TNF-α

production on LPS-stimulated RAW264.7 macrophages, and it showed certain inhibition activity with IC_{50} of 38.18 [8].

Although natural products **1** and **2** exhibit a broad spectrum of interesting biological activities, the detailed pharmacological studies of these compounds so far have been minimal. Such studies are limited since glycosides **1** and **2** were isolated in low yields from natural sources, and syntheses of them and their derivatives were rarely reported. Hence, short and efficient routes to obtain **1** and **2** are urgently required. We herein report an efficient and scalable methodology to synthesize natural products **1** and **2,** which also can be applied for the synthesis of diverse derivatives of these molecules in the future.

2. Results and discussion

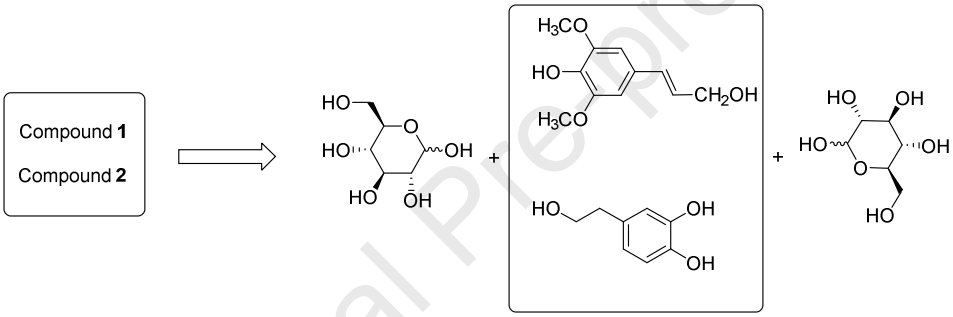
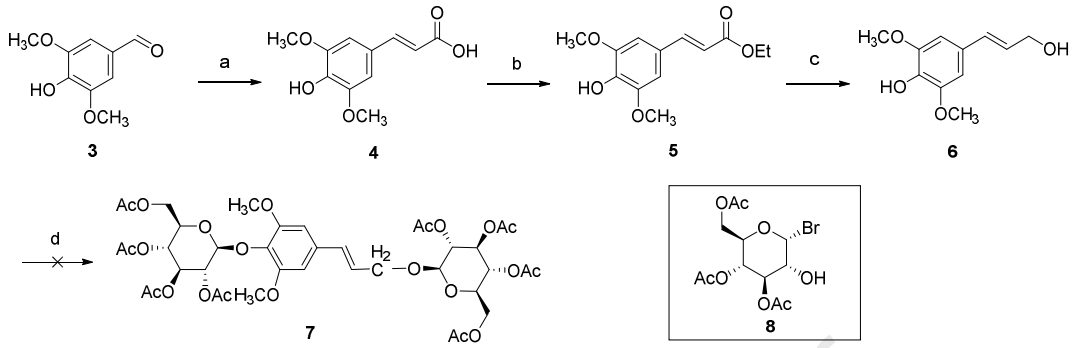


Figure 2. Retrosynthetic approaches to compounds **1** and **2**

Through investigating of their structures, we have noticed that both **1** and **2** contained three main groups, including two β-$_D$-glucose rings and one phenylpropanoid aglycone (for compound **1**) or phenylethanol aglycone (for compound **2**). Hence, highly regioselective glycosylations of these two different active aglycones would be the key steps of our devising synthetic routes (**Figure 2**).

As shown in **Scheme 1**, our strategy for total synthesis of glycoside **1** started from commercially available Syringaldehyde (**3**). A 3-step synthesis that utilized Knoevenagel reaction, ethyl esterification, and $LiAlH_4$ reduction was taken to generate Sinapyl alcohol (**6**) following the method that previously reported [9, 10]. With the key intermediate **6** in hand, our synthesis route towards intermediate **7** was devised by coupling **6** and excess glycosyl donor 2,3,4,6-tetra-*O*-acetyl-a-$_D$-glucopyranosyl bromide (**8**), which was readily got in a 3-step sequence from $_D$-glucose, under Koenigs-Knorr conditions [11]. The reaction was conducted in dry CH_2Cl_2 for 10 h under dark in the presence of Ag_2CO_3 and powdered 4 Å MS (molecular sieve) that was dried at 400 °C for 8 h before usage. However, the attempted double-glycosylation of acceptor **6**

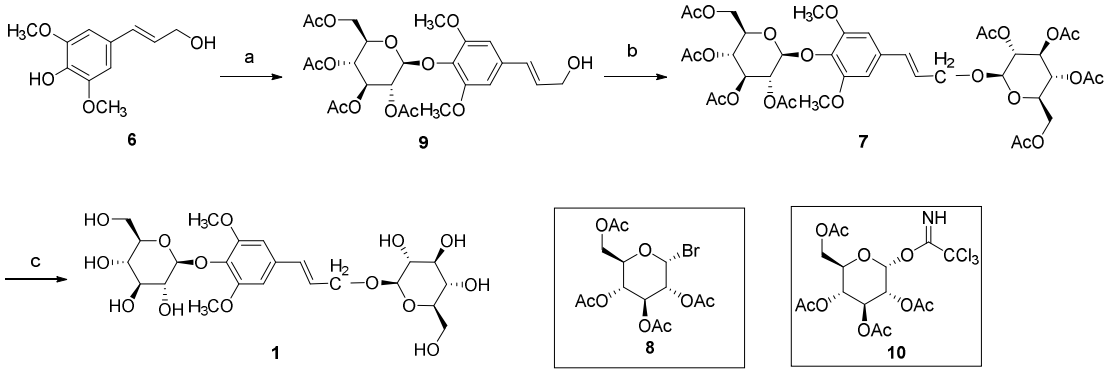
with an excessive amount of donor **9** (10 equiv.) provided a complex mixture, from which product **7** could not be isolated.



Scheme 1. Design of Initial Attempt to Prepare Compound **7**. Reaction and Conditions: (a) Malonic acid, pyridine, *p*-aminotoluene, piperazine, toluene, 80 ºC, 83.7%; (b) *p*-Toluenesulfonic acid, alcohol, 75 ºC, 76.5%; (c) $LiAlH_4$, BnCl, THF, room temperature, 82.8%; (d) 4Å MS, Ag_2CO_3, CH_2Cl_2, r.t.

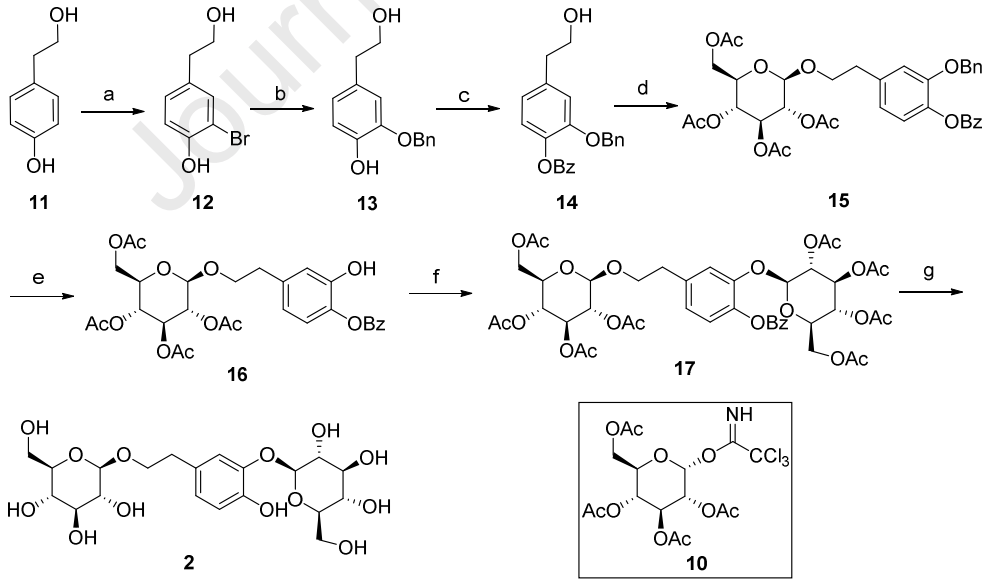
Then the synthetic route was modified. In the modified route, two separate glycosylation steps were required in order to obtain **7** from **6**. As phenolic hydroxyl of **6** could be ionized in the weak alkali reaction medium while the alcoholic hydroxyl could not, the phenolic hydroxyl of **6** was selectively coupled to acetyl-1-bromoglucose (**8**) in the presence of K_2CO_3 and phase transfer catalyst (PTC, tetrabutylammonium bromide, TBAB) in CH_2Cl_2-water solvent system without any protective groups to generate compound **9** successfully [12]. Efforts to obtain **7** from **9** under Koenigs-Knorr conditions described above, however, gave poor yields (31%). To improve the yield, we next turned to Schmidt's trichloroacetimidate procedure. Accordingly, glycosyl donor trichloroacetimidate **10** was prepared from D-glucose following literature procedure [13]. TMSOTf-promoted glycosylation of compound **9** using **10** proceeded stereoselectively and the *β*-anomer of glycoside **7** was obtained in 71.6% yield.

The final deprotection step involving the cleavage of all the acetyl groups by $NaOCH_3$ afforded natural product **1** in high yield (75.0%). The ^1H NMR and ^{13}C NMR spectra of the synthetic compound **1** matched the published data [3].



Scheme 2. Synthesis of Isosyringinoside (**1**). Reaction and Conditions: (a) Compound **8**, TBAB, K_2CO_3, CH_2Cl_2-H_2O, r.t., 71.1%; (b) (i) Compound **10**, 4Å MS, TMSOTf, CH_2Cl_2, -80 ºC, 71.6% or (ii) Compound **8**, 4Å MS, Ag_2CO_3, CH_2Cl_2, r.t., 31.2%; (c) CH_3ONa, CH_3OH, 75.0%.

As shown in **scheme 3**, the first step of the total synthesis for natural product **2** was bromination of 4-hydroxyphenethyl alcohol **11**. Using a known method [14], compound **12** was obtained in 89.4% yield. Then a Cu-catalyzed C-O bond-forming reaction of aryl bromide **12** and benzyl alcohol was taken to get compound **13**, which was subsequently converted to its benzoate derivative **14** (77.5% yield) using benzoic acid anhydride. The glycosylation of protected hydroxytyrosol **14** with trichloroacetimidate **10** processed stereoselectively, and the *β*-anomer of glycoside **15** was isolated in satisfactory yield (74.0 %).



Scheme 3. Synthesis of 3-(*O*-*β*-$_D$-glucopyranosyl)-α-(*O*-*β*-$_D$-glucopyranosyl)-4-hydroxy phenylethanol (**2**). Reaction and Conditions: (a) NaBr, Oxone, H_2O, acetone, 0 ºC; 89.4%; (b) CuI, K_3PO_4, 8-hydroxyquinoline, benzyl alcohol, 110 ºC, 85.7%; (c) Benzoic acid anhydride, DMAP, Et_3N, CH_2Cl_2, 0 ºC, 77.5%; (d) Compound **10,** 4Å MS, TMSOTf, CH_2Cl_2, -78 ºC~-20 ºC, 74.0 %;

(e) 10% Pd/C, H_2, CH_3OH/THF, 95.8%; (f) Compound **10,** 4Å MS, BF_3-$(CH_3CH_2O)_2$, CH_2Cl_2, -78 ºC~-20 ºC, 75.6 %; (g) CH_3ONa, CH_3OH, 84.8%.

In the next step, Pd/C catalytic system under H_2 atmosphere was used to deprotect benzyl protection of phenol to obtain **16** successfully. However, our attempts to glycosylate compound **16** with bromide **4** under the above PTC conditions failed, proving that the hydroxy group of **16** was much more inert than the phenolic hydroxyl of **6**. Instead, compound **16** was treated with trichloroacetimidate **10** in the presence of BF_3-$(C_2H_5)_2O$, which had been confirmed as a better catalyst than TMSOTf for formation of phenolic *O*-glycosylatic bond [15], to get **17** in 75.6% yield. Finally, the deprotection of the sugar moiety (acetate cleavages) and phenol (benzoate cleavage) of compound **17** proceeded smoothly and the desired target glycoside **2** was isolated in high yield (84.8%).

Based on the synthesis routes presented above, the key steps of the processes are different *O*-glycosylations, including BF_3-$O(C_2H_5)_2$ and TMSOTf catalyzed glycosylations with **10** and PTC promoted glycosylation with **8**. The glycosylations of these receptors (compounds **6**, **9**, **14** and **16**) with glycosyl donors (compounds **8** and **10**) led to the desired *β-O*-glucosides (**9**, **7**, **15** and **17**) in complete stereoselectivity with good yields (71.1%-75.6%). The structures of all *β*-anomers were confirmed by the presence of a doublet of the anomeric proton with characteristic vicinal interaction constants ($^3J_{1,2}$ and $^3J_{1',2'}$) in the interval of 7.2-8.0 Hz in the ^{1}H NMR spectra.

3. Conclusion

In summary, we have accomplished the first total syntheses of Isosyringinoside (**1**) and 3-(*O*-*β*-$_D$-glucopyranosyl)-*α*-(*O*-*β*-$_D$-glucopyranosyl)-4-hydroxy phenylethanol (**2**). Synthesis of **1** utilized a six-step sequence from commercially available Syringaldehyde (**3**) and gave **1** in an overall yield of 20.2%. Compound **2** was obtained via a seven-step synthesis route in the overall yield of 27.0%. This efficient and scalable methodology should be of benefit for further biological investigations on this kind of natural products.

4. Experimental

4.1 General experimental procedure.

Melting points were measured on X-4 digital display microscopic melting point apparatus (Tianjin Xintian Optical Analytical Instruments Co. Ltd. Tianjin, China) and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance 400 (Bruker Co., Fallanden,

Switzerland) instrument or JEOL Eclips-600 (Japan Electronics Co. Ltd. Tokyo, Japan). Optical rotations were recorded on a Jasco P-1020 prolarimeter. HR-MS were obtained on Bruker Apex II mass spectrometer (Bruker Co., Bremen, Germany). The solvents were analytical grade and newly distilled before usage.

*4.2 3-(4-Hydroxy-3,5-dimethoxyphenyl)acrylic acid (**4**)*

A mixture of 4-hydroxy-3,5-dimethoxybenzaldehyde (**3**, 10 g, 54.9 mmol) , malonic acid (6.29 g, 60.4 mmol), pyridine (3.62 g, 45.7 mmol), *p*-aminotoluene (0.59 g,0.55 mmol) and piperazine (0.1 g, 1.1 mmol) in toluene (150 ml) was stirred at 80 ºC for 3 h. After the mixture was cooled to room temperature, a solution of aq. 25% K_2CO_3 (75 ml) was added and the mixture was stirred for another 10 min. Then separated, the aqueous layer was adjusted to pH 2.5 with conc. HCl and the powder precipitated from the aqueous solution was collected by filtration and washed with water to give the compound **4** (10.3 g, 83.7% yield) as a light yellow powder. M.p. 193.5-195.0 ºC. ^{1}H NMR (DMSO-d_6) δ: 12.16 (s, 1H, -COOH), 8.93 (s, 1H, Ph-OH), 7.49 (d, *J* = 15.8 Hz, 1H, -CH=CH-), 6.99 (s, 2H, -PhH), 6.42 (d, *J* = 15.8 Hz, 1H, -CH=CH-), 3.80 (s, 6H, -OCH_3). ^{13}C NMR (DMSO-d_6) δ: 167.9 (-CO), 147.9, 144.8 (-CH=CH-), 137.9, 124.5, 116.0 (-CH=CH-), 105.9, 56.0 (-OCH_3). ^{1}H NMR and ^{13}C NMR are in agreement with the reported values [10].

*4.3 Ethyl 3-(4-hydroxy-3,5-dimethoxyphenyl)acrylate (**5**)*

A solution of **4** (10.3 g, 45.9 mmol) and *p*-toluenesulfonic acid (0.79 g, 4.6 mmol) in alcohol (100 ml) was heated at 75 ºC for 20 h. After the mixture was cooled to room temperature, alcohol was removed by evaporation under reduced pressure. The residue was dissolved in EtOAc (200 ml) and washed with aq. 5 % Na_2CO_3 and brine, then evaporated in vacuo and recrystallized from EtOAc and *n*-hexane (V/V, 1:10) to afford compound **5** (8.8 g, 76.5% yield) as a white solid. M.p. 83.2-86.5 ºC. ^{1}H NMR ($CDCl_3$) δ: 7.60 (d, *J* = 15.9 Hz, 1H, -CH=CH-), 6.77 (s, 2H, Ph-H), 6.31 (d, *J* = 15.9 Hz, 1H, -CH=CH-), 4.26 (q, *J* = 7.1 Hz, 2H, -OCH_2-), 3.91 (s, 6H, -OCH_3), 1.34 (t, *J* = 7.1 Hz, 3H, -CH_3). ^{13}C NMR ($CDCl_3$) δ: 167.2 (-CO), 147.2, 144.9 (-CH=CH-), 137.1, 125.9, 115.9 (-CH=CH-), 105.0, 60.4 (-OCH_2-), 56.3 (-OCH_3), 14.4 (-CH_3). ^{1}H NMR and ^{13}C NMR are in agreement with the reported values [16].

*4.4 4-(3-hydroxyprop-1-en-1-yl)-2,6-dimethoxyphenol (**6**)*

To a stirred suspension of $LiAlH_4$ (0.57 g, 15 mmol) in dry THF (40 ml), a solution of BnCl (1.98 g, 15 mmol) in dry THF (10 ml) was added. After the suspension was stirred for 15 min. A solution of **5** (2.52 g, 10 mmol) in dry THF (15 ml) was added dropwise at r.t. Then the reaction mixture was stirred for 1.5 h. After reaction was completed (detected by TLC), 20 ml water was added to quench the reaction. Then the mixture was extracted with EtOAc (50 ml ×3). The organic phase was combined and washed with brine, dried over Na_2SO_4, evaporated under vacuum to give crude product **6** (1.74 g, 82.8% yield) as an colourless oil. Compound **6** can be introduced to next step without further purification.

*4.5 (E)-4-(3-hydroxyprop-1-enyl)-2,6-dimethoxyphenyl 2,3,4,6-tetra-O-acetyl-β-$_D$-glucopyranoside (**9**)*

To a solution of **6** (1.5 g, 7.1 moml) in CH_2Cl_2 (25 ml) was added aq. 20% K_2CO_3 (15 ml) and TBAB (2.3 g, 7.1 mmol), then the mixture stirred vigorously at room temperature for 10 min. After that compound **8** (4.4 g, 10.7 mmol) was added and stirred at room temperature for anther 5 h. The mixture was diluted with CH_2Cl_2 (100 ml), washed with brine, and dried over $MgSO_4$. The solvent was evaporated under vacuum. The residue was purified by chromatography on silica gel (gradient eluent of EtOAc/petroleum ether, 1:1) to give compound **9** (2.7 g, 71.1% yield) as a light yellow solid. M.p. 76.0-79.6 ºC. $[a]_D$ -28 º (c = 0.11, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 6.60 (s, 2H, Ph-H), 6.53 (d, *J* = 15.9 Hz, 1H, -CH_2=CH_2-), 6.29 (dt, *J* = 15.9, 5.6 Hz, 1H, -CH_2=CH_2-), 5.41-5.20 (m, 3H, H-2, H-3, H-4), 5.07 (d, *J* = 7.2 Hz, 1H, H-1), 4.32 (d, *J* = 5.6 Hz, 2H, -CH_2OH), 4.26 (dd, *J* = 12.2, 5.0 Hz, 1H, H-6a), 4.12 (dd, *J* = 12.2, 2.5 Hz, 1H, H-6b), 3.83 (s, 6H, -OCH_3), 3.69 (ddd, *J* = 9.1, 5.0, 2.5 Hz, 1H, H-5), 2.04-2.03 (m, 12H, -Ac). ^{13}C NMR ($CDCl_3$) δ: 170.7 (-CO), 170.5 (-CO), 169.5(-CO), 169.4(-CO), 153.0, 134.1, 133.7, 130.5, 128.8, 103.7, 101.3 (C-1), 73.0, 72.0, 71.9, 68.5, 63.4, 62.3, 56.2 (-OCH_3), 20.7 (-CH_3), 20.7 (-CH_3), 20.7 (-CH_3), 20.6 (-CH_3). ^{1}H NMR and ^{13}C NMR are in agreement with the reported values [17].

*4.6 (E)-4-[3-(2,3,4,6-tetra-O-acetyl-$_D$-glucopyranosyloxy)prop-1-enyl]-2,6-dimethoxyphenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (**7**)*

A mixture of trichloroacetimidate **10** 1.82 g (3.7 mmol) and compound **9** 1.32 g (2.4 mmol) and activated 4 Å molecular sieves (2 g) in DCM (20 mL) was stirred for 30 min at −20 °C under argon atmosphere, then cooled to −78 °C and TMSOTf (cat., 0.05 ml) was added and the stirring was continued for further 30 min after which the temperature was brought up to −20 °C. The

reaction mixture was neutralized by addition of Et_3N, washed with brine, dried with anhydrous Na_2SO_4 and evaporated in vacuo. The crude product was purified by column chromatography (EtOAc/petroleum ether, 1:2) to give a colourless oil **7** 1.44 g (71.6%). $[a]_D$ -13 º (c = 0.13, $CHCl_3$). ESIHRMS m/z 871.2847 $[M+H]^+$ (calcd for $C_{39}H_{51}O_{22}^+$ 871.2866). ^{1}H NMR ($CDCl_3$) δ: 6.56 (s, 2H, Ph-H), 6.47 (d, *J* = 15.8 Hz, 1H, -CH_2=CH_2-), 6.12 (dt, *J* = 15.8, 5.6 Hz, 1H, -CH_2=CH_2-), 5.33-5.16 (m, 4H, H-2, H-4, H-2', H-4',), 5.10 (t, *J* = 9.7 Hz, 1H, H-3), 5.05-5.03 (m, 2H, H-3', H-1), 4.59 (d, *J* = 7.9 Hz, 1H, H-1'), 4.47 (m, 1H, H-6a'), 4.24-4.22 (m, 2H, H-6b', H-6a), 4.16-4.13 (m, 1H, H-6b), 4.11-4.08 (m, 2H, -CH_2O-), 3.80 (s, 6H, -OCH_3), 3.72-3.61 (m, 2H, H-5, H-5'), 2.06 (s, 3H, -Ac), 2.03 (s, 3H, -Ac), 2.02 (s, 3H, -Ac), 2.01 (s, 3H, -Ac), 2.01 (s, 6H, -Ac), 2.00 (s, 3H, -Ac), 1.99 (s, 3H, -Ac). ^{13}C NMR ($CDCl_3$) δ: 170.8 (-CO), 170.7 (-CO), 170.5 (-CO), 170.4 (-CO), 169.5 (-CO), 169.5 (-CO), 169.4 (-CO), 169.4 (-CO), 153.1, 134.5, 133.4, 132.7, 124.7, 103.9, 101.4 (C-1), 99.8 (C-1'), 73.1, 72.9, 72.0, 71.9, 71.4, 69.9, 68.5, 68.4, 62.3, 62.0, 60.5, 56.4, 20.8 (3 × C, -Ac), 20.8 (-Ac), 20.8 (-Ac), 20.7 (-Ac), 20.7 (-Ac), 20.7 (-Ac).

*4.7 Isosyringinoside (**1**)*

To a solution of CH_3ONa (0.32 g, 6 mmol) in 100 ml CH_3OH was added compound **7** (0.65 g, 0.75 mmol). The mixture stirred at room temperature for 1.5 h. After the reaction was completed (detected by TLC), Amberlite IR 120 (5 g) was added and stirred for another 20 min. Then the mixture was filtered and evaporated to give a solid residue, which was recrystallized from alcohol to get compound **1** 0.30 g (75.0% yield) as a white powder. M.p. 190.1-196.3 ºC. $[\alpha]_D$ = - 44 (c 0.16, MeOH). ESIHRMS m/z 557.1840 $[M+Na]^+$ (calcd for $C_{23}H_{34}NaO_{14}^+$ 557.1845). ^{1}H NMR (CD_3OD) δ: 6.77 (s, 2H, Ph-H), 6.62 (t, *J* = 15.9 Hz, 1H, -CH_2=CH_2-), 6.34 (dt, *J* = 15.9, 6.1 Hz, 1H, -CH_2=CH_2-), 4.87 (d, 1H, *J* = 7.3 Hz, H-1), 4.52 (dd, *J* = 14.0, 5.0 Hz, 1H, one hydrogen atom of -CH_2O-), 4.37 (d, *J* = 7.8 Hz, 1H, H-1'), 4.33 (dd, *J* = 14.0, 6.5 Hz, 1H, one hydrogen atom of -CH_2O-), 3.86 (s, 6H, -OCH_3), 3.90-3.85 (m, 1H, H-6a'), 3.80-3.76 (m, 1H, H-6a), 3.70-3.64 (m, 2H, H-6b, H-6b'), 3.48-3.34 (m, 4H, H-2, H-3, H-4, H-2'), 3.29-3.20 (m, 4H, H-5, H-3', H-4', H-5'). ^{13}C NMR (CD_3OD) δ: 154.4, 136.0, 135.3, 133.6, 127.0, 105.7, 105.4 (C-1), 103.4 (C-1'), 78.4, 78.2, 78.1, 77.9, 75.8, 75.3, 71.8, 71.3, 71.0, 62.9, 62.5, 57.3 (-OCH_3).

*4.8 2-Bromo-4-(2-hydroxyethyl)phenol (**12**)*

To a solution of hydroxyphenethyl alcohol **11** (13.8 g，0.1 mol) in acetone (150 ml) were added NaBr (12.3 g, 12 mmol). Then a solution of Oxone in water (10 ml) was added at 0 ºC in a

period of 15 min. The reaction mixture was kept at 0 ºC and stirred for 1.5 h. The reaction was quenched by $Na_2S_2O_3$ and extracted with ethyl acetate (3 × 100 ml). The combined organic layers were washed with brine (100 ml), dried over Na_2SO_4, and evaporated in vacuo. The crude residue was crystallized from ethyl acetate/n-hexane to give pure **12** as crystals (19.4 g, 89.4% yield). M.p. 90.0-94.0 ºC. ^{1}H NMR ($CDCl_3$) δ: 7.33 (d, *J* = 2.1 Hz, 1H, Ph-H), 7.07 (dd, *J* = 8.3, 2.1 Hz, 1H, Ph-H), 6.95 (d, *J* = 8.3 Hz, 1H, Ph-H), 5.44 (s, 1H, -OH), 3.81 (dd, *J* = 12.3, 6.5 Hz, 2H, -CH_2OH), 2.77 (t, *J* = 6.5 Hz, 2H, Ph-CH_2-). ^{13}C NMR (CD_3OD) δ: 152.6, 133.4, 132.3, 129.6, 116.6, 109.6, 62.66 (-CH_2OH), 38.1 (-CH_2-). ^{1}H NMR and ^{13}C NMR are in agreement with the reported values [18].

*4.9 2-(Benzyloxy)-4-(2-hydroxyethyl)phenol (**13**)*

A mixture of compound **12** (5.0 g, 23.0 mmol), CuI 0.22 g (1.2 mmol, 5 mol%), 8-hydroxyquinoline 1.0 g (2.3 mmol, 10 mol %), and K_3PO_4 (9.7 g, 46.7 mmol) were added to a screw-capped Schlenk tube under argon. The tube was then evacuated and back filled with argon (3 cycles). Benzyl alcohol 23 ml were added by syringe at room temperature. The reaction mixture was stirred at 110 °C for 24 h then allowed to reach room temperature and diluted with dichloromethane (100 ml). The slurry was filtered and the filter cake was washed with 100 mL of dichloromethane. The solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel with ethyl acetate/petroleum ether 1:4 as eluent, to afford the desired product **13** 4.8 g (85.7 %) as a white solid. M.p. 110.1-116.3 °C. ESIHRMS m/z 245.1169 $[M+H]^+$ (calcd for $C_{15}H_{17}O_3^+$ 245.1172). ^{1}H NMR ($CDCl_3$) δ: 7.50-7.29 (m, 5H, Ph-H), 6.88 (d, *J* = 8.0 Hz, 1H, Ph-H), 6.80 (d, *J* = 1.8 Hz, 1H, Ph-H), 6.73 (dd, *J* = 8.0, 1.8 Hz, 1H, Ph-H), 5.72 (s, 1H, -OH), 5.08 (s, 2H, PhCH_2O-), 3.78 (m, 2H, -CH_2OH), 2.76 (t, *J* = 6.5 Hz, 2H, -CH_2-). ^{13}C NMR ($CDCl_3$) δ: 145.9, 144.6, 136.4, 130.3, 128.8, 128.6, 128.0, 122.1, 114.9, 113.1, 71.2 (PhCH_2O-), 63.9 (-CH_2OH), 38.8 (-CH_2-).

*4.10 2-(benzyloxy)-4-(2-hydroxyethyl)phenyl benzoate (**14**)*

A 500 ml flask was charged with **13** 5.0 g (20.5 mmol), CH_2Cl_2 (150 ml), Et_3N (40 mmol, 5.5 ml) and DMAP (4 mmol, 0.5 g), benzoic acid anhydride 3.9 ml (4.7 g, 21 mmol) in 50 ml CH_2Cl_2 was added dropwise to the mixture at 0 °C. The mixture was allowed to stir at room temperature for 10 min until all of the starting material disappeared. Then, the mixture was poured into water (100 mL), extracted with EtOAc (150 ml), washed with 1 N HCl (100 ml) and brine (100 ml), and

dried over Na_2SO_4. The crude organic phase was concentrated in vacuo and purified with column chromatography (silica gel, ethyl acetate/petroleum ether = 5:1) to afford the corresponding product **14** (5.5 g, 77.5%) as a white solid. M.p. 41.0-44.0 °C. ESIHRMS m/z 349.1430 $[M+H]^+$ (calcd for $C_{22}H_{21}O_4^+$ 349.1434). ^{1}H NMR ($CDCl_3$) δ: 8.21 (dd, *J* = 8.5, 1.5 Hz, 2H, Ph-H), 7.63-7.60 (m, 1H, Ph-H), 7.50-7.48 (m, 2H, Ph-H), 7.31-7.29 (m, 2H, Ph-H), 7.26-7.20 (m, 3H, Ph-H), 7.12 (d, *J* = 8.1 Hz, 1H, Ph-H), 6.91 (d, *J* = 2.3 Hz, 1H, Ph-H), 6.86 (dd, *J* = 8.1, 2.3 Hz, 1H, Ph-H), 5.10 (s, 2H, $PhCH_2O$-), 3.81 (t, *J* = 6.8 Hz, 2H, -CH_2OH), 2.83 (t, *J* = 6.8 Hz, 2H, -CH_2-). ^{13}C NMR ($CDCl_3$) δ: 165.2 (C=O), 150.3, 139.2, 137.7, 136.7, 133.6, 130.4, 128.6, 128.5, 127.8, 127.0, 123.0, 121.8, 115.3, 70.7 ($PhCH_2O$-), 63.6 (-CH_2OH), 39.2 (-CH_2-).

*4.11 2-(4-Benzoyloxy-3-benzyloxyphenyl)ethyl 2,3,4,6-tetra-O-acetyl-β-$_D$-glucopyranoside (**15**)*

A mixture of **14** (3.48 g, 10 mmol), **10** (7.39 g, 15 mmol), and 4Å molecular sieves (6.0 g) were added to dry CH_2Cl_2 (300 ml) under argon atmosphere at -78 °C. The mixture was stirred for 30 min and TMSOTf (cat., 0.1 ml) was added. Then the stirring was continued for further 30 min after which the temperature was brought up to 0 °C. The reaction mixture was neutralized by addition of Et_3N and concentrated. The crude product was purified by column chromatography (petroleum ether: EtOAc 1:2 V/V) to give **15** (5.02 g, 74.0%) as colourless oil. $[a]_D$ -33.8 (c = 0.4, $CHCl_3$). ESIHRMS m/z 679.2369 $[M+H]^+$ (calcd for $C_{36}H_{39}O_{13}^+$ 679.2385). ^{1}H NMR ($CDCl_3$) δ: 8.18 (dd, *J* = 8.3, 1.2 Hz, 2H, Ph-H), 7.61-7.46 (m, 3H, Ph-H), 7.31-7.22 (m, 5H, Ph-H), 7.08 (d, *J* = 8.1 Hz, 1H, Ph-H), 6.89 (d, *J* = 1.8 Hz, 1H, Ph-H), 6.82 (dd, *J* = 8.1, 1.8 Hz, 1H, Ph-H), 5.19-4.98 (m, 5H, H-2, H-3, H-4, $PhCH_2O$-), 4.45 (d, *J* = 8.0 Hz, 1H, H-1), 4.26 (dd, *J* = 12.3, 4.7 Hz, 1H, H-6a), 4.14-4.12 (m, 2H, H-6b, one hydrogen atom of -CH_2O-), 3.68 (ddd, *J* = 10.0, 4.7, 2.4 Hz, 1H, H-5), 3.63 (m, 1H, one hydrogen atom of -CH_2O-), 2.87-2.85 (m, 2H, -CH_2-), 2.08 (s, 3H, -Ac), 2.01 (s, 3H, -Ac), 1.99 (s, 3H, -Ac), 1.91 (s, 3H, -Ac). ^{13}C NMR ($CDCl_3$) δ: 170.8, 170.4, 169.6, 169.5, 165.0, 150.1, 139.1, 137.5, 136.9, 133.5, 130.3, 129.6, 128.6, 128.4, 127.7, 127.0, 122.8, 121.6, 115.3, 100.9 (C-1), 72.8, 71.9, 71.1, 70.7, 70.6, 68.5, 62.0, 36.0, 20.9, 20.7, 20.7, 20.6.

*4.12 2-(4-Benzoyloxy-3-hydroxyphenyl)ethyl 2,3,4,6-tetra-O-acetyl-β-$_D$-glucopyranoside (**16**)*

A suspension of **15** (2 g, 2.9 mmol) and palladium (100 mg, 10 wt % on activated carbon) in a mixture of THF : CH_3OH = 1 : 1 (100 ml) was stirred at room temperature under H_2 atmosphere

for 24 h. The reaction mixture was filtered through a pad of Celite. The filtrate was then concentrated in vacuo to generate crude product **16** (1.63 g, 95.8%) as a white solid.

*4.13 2-[4-Benzyloxy-3-(2,3,4,6-tetra-O-acetyl-β-$_D$-glucopyranosyloxy)]ethyl 2,3,4,6-tetra-O-acetyl-β-$_D$-glucopyranoside (**17**)*

A mixture of trichloroacetimidate **10** 2.0 g (4.1 mmol) and compound **16** 1.24 g (2.1 mmol) and activated 4 Å molecular sieves (1.0 g) in dry DCM (50 ml) was stirred for 30 min at −20 °C under argon atmosphere, then cooled to −78 °C and TMSOTf (cat., 0.05 ml) was added and the stirring was continued for further 30 min after which the temperature was brought up to −20 °C. The reaction mixture was neutralized by addition of Et_3N, washed with brine, dried with anhydrous Na_2SO_4 and evaporated in vacuo. The crude product was purified by column chromatography (EtOAc/petroleum ether, 1:2) to give **17** 2.8 g (75.6%) as colourless oil. $[a]_D$ -21 (c = 0.2, $CHCl_3$). ESIHRMS m/z 919.2848 $[M+H]^+$ (calcd for $C_{43}H_{51}O_{22}^+$ 919.2867). ^{1}H NMR ($CDCl_3$) δ: 8.13 (d, *J* = 7.1 Hz, 2H, Ph-H), 7.64 (t, *J* = 7.4 Hz, 1H, Ph-H), 7.51 (t, *J* = 7.7 Hz, 2H, Ph-H), 7.07 (d, *J* = 8.1 Hz, 1H, Ph-H), 6.99 (d, *J* = 1.8 Hz, 1H, Ph-H), 6.93 (dd, *J* = 8.2, 1.8 Hz, 1H, Ph-H), 5.41-4.83 (m, 7H, H-2, H-3, H-4, H-1', H-2', H-3', H-4'), 4.47 (d, *J* = 7.9 Hz, 1H, H-1), 4.36-4.08 (m, 5H, one hydrogen atom of -CH_2O-, H-6, H-6'), 3.97 (ddd, *J* = 10.0, 4.8, 2.3 Hz, 1H, H-5'), 3.77-3.56 (m, 2H, H-5, one hydrogen atom of -CH_2O-), 2.88 (t, *J* = 6.0 Hz, 2H, -CH_2-), 2.10 (s, 3H, -Ac), 2.06 (s, 3H, -Ac), 2.04 (s, 3H, -Ac), 2.03 (s, 3H, -Ac), 2.02 (s, 3H, -Ac), 1.92 (s, 3H, -Ac), 1.89 (s, 3H, -Ac), 1.76 (s, 3H, -Ac). ^{13}C NMR ($CDCl_3$) δ: 170.7, 170.6, 170.3, 170.2, 169.6, 169.5, 169.4, 169.0, 164.7, 148.0, 138.9, 137.9, 133.6, 130.3, 129.2, 128.5, 123.7, 123.2, 117.8, 100.7 (C-1), 98.4 (C-1'), 72.9, 72.6, 71.9, 71.8, 70.9, 70.8, 70.2, 68.5, 68.2, 68.1, 61.9, 35.9, 20.8, 20.7, 20.7, 20.6 (2 × C), 20.5, 20.5, 20.2.

*4.14 3-(O-β-$_D$-glucopyranosyl)-α-(O-β-$_D$-glucopyranosyl)-4-hydroxy phenylethanol (**2**)*

Compound **17** 0.63 g (0.69 mmol) was dissolved in 60 ml of a mixture of CH_3OH/THF (50:50). Then CH_3Na 120 mg was added. When the deprotection was completed, the solution was neutralized by adding 5 g of an ion-exchange resin. The agitation was maintained for 10 min, and then the filtered. The methanol was eliminated by vacuum evaporation to afford a white solid, which was recrystallized from alcohol to get compound **2** (0.28 g, 84.8%). M.p. 73.2-78.6 °C. $[\alpha]_D$ = -45 (c 0.12, MeOH). ESIHRMS m/z 501.1581 $[M+Na]^+$ (calcd for $C_{20}H_{30}NaO_{13}^+$, 501.1579). ^{1}H NMR (CD_3OD) δ: 7.10 (d, *J* = 1.9 Hz, 1H, Ph-H), 6.79 (dd, *J* = 8.1, 1.9 Hz, 1H, Ph-H), 6.74 (d, *J*

= 8.1 Hz, 1H, Ph-H), 4.76 (d, *J* = 7.4 Hz, 1H, H-1), 4.27 (d, *J* = 7.8 Hz, 1H, H-1'), 4.08-4.03 (m, 1H, one hydrogen atom of -CH_2O-), 3.90 (dd, *J* = 12.1, 2.2 Hz, 1H, H-6a), 3.86 (dd, 12.1, 2.3 Hz, 1H, H-6a'), 3.70-3.65 (m, 3H, H-6b, H-6b', one hydrogen atom of -CH_2O-), 3.50-3.47 (m, 2H, H-2, H-3'), 3.45-3.42 (m, 1H, H-5'), 3.39-3.33 (m, 2H, H-4, H-5), 3.30-3.29 (m, 1H, H-4'), 3.27-3.25 (m, 1H, H-3), 3.17 (dd, *J* = 9.2, 7.8 Hz, 1H, H-2'), 2.82 (t, *J* = 7.4 Hz, 2H, -CH_2-). ^{13}C NMR (150 MHz, CD_3OD) δ: 146.6, 146.4, 131.7, 125.1, 119.4, 116.8, 104.3 (C-1'), 104.2 (C-1), 78.2, 78.0, 77.8, 77.6, 75.0, 74.8, 71.7, 71.6, 71.4, 62.7, 62.5, 36.4.

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The total syntheses of two natural bioactive glycosides, Isosyringinoside (**1**) and 3-(*O*-*β*-$_D$-glucopyranosyl)-α-(*O*-*β*-$_D$-glucopyranosyl)-4-hydroxy phenylethanol (**2**), were firstly reported in short, convenient routes.

Conflict of interest

We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

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