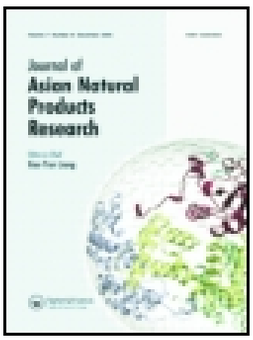

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Total synthesis of three natural phenethyl glycosides

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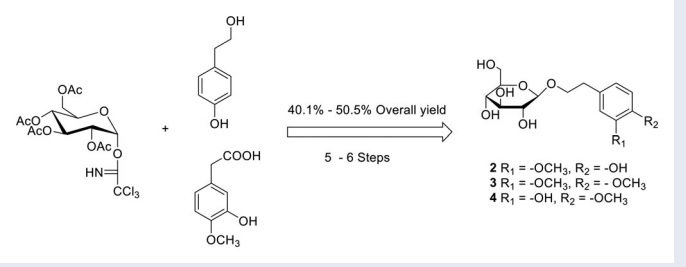
ABSTRACT

Phenethyl glycosides having phenolic or methoxy functions at benzene rings are substances widely occurring in nature. This kind of compounds has been shown to have anti-oxidant, anti-inflammatory, and anticancer activities. However, some of them are not naturally abundant, thus the synthesis of such molecules is desirable. In this paper, natural phenethyl glycosides **3** and **4** were first totally synthesized from easily available materials with overall yields of 50.5% and 40.1%, respectively. And a new synthetic route to obtain natural phenethyl glycoside **2** in 46.2% yield was also described.



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Total synthesis; phenethyl glycosides; natural product

1. Introduction

Phenethyl glycosides having phenolic or methoxy functions at benzene rings are substances widely occurring in nature (Figure 1). The most famous compound among this kind of natural products is salidroside **1**, which is isolated from *Rhodiola sachalinensis* A. Bor. Salidroside **1** has a wide range of pharmacological effects, such as anti-oxidant, anti-inflammatory, anticancer, hepatoprotective, cardioprotective, neuroprotective, antidiabetic, and antiviral activities [1–5]. So the total syntheses of salidroside **1** employing various chemical or enzymatic methods have been previously reported.

As shown in Figure 1, natural phenethyl glycosides **2** [(2R,3R,4S,5S,6R)-2-(4-hydroxy-3-methoxyphenethoxy)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol], **3**

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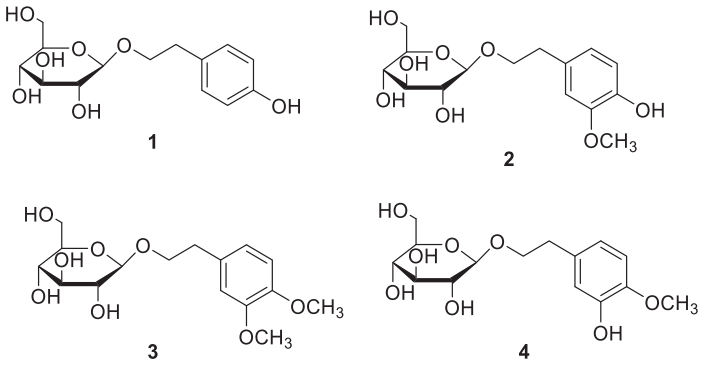


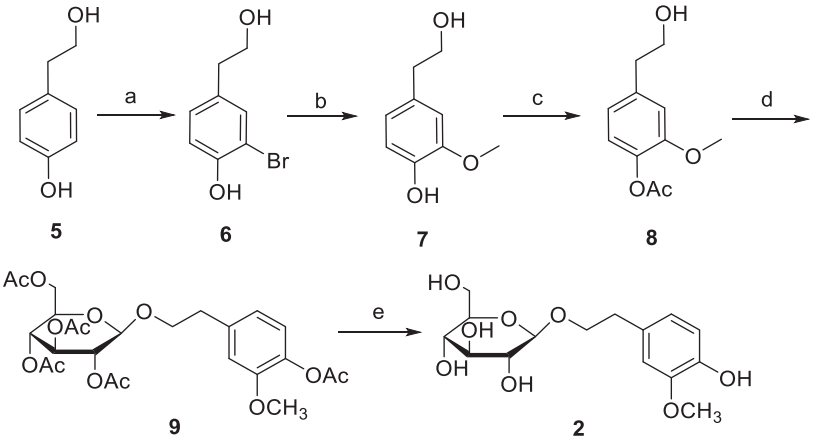
Figure 1. Structures of salidroside **1** and natural products **2**–**4**.

[(2R,3R,4S,5S,6R)-2-(3,4-dimethoxyphenethoxy)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol], and **4** [(2R,3R,4S,5S,6R)-2-(3-hydroxy-4-methoxyphenethoxy)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol] have chemical structures similar to salidroside **1**. They were first isolated from polar fraction of *Saussurea genus* (Asteraceae), leaves of *Forsythia suspensa* (Lauraceae), and dried root of *Scrophularia ningpoensis,* respectively [6–8]. These compounds have attracted scientific attention as a result of their diverse biological activities, which include antibacterial [7], inhibiting nitric oxide production [9], and cell protection [10]. However, all of these compounds have been isolated in low yields from natural sources and synthesis of them are rarely reported [11, 12]. So far detailed pharmacological study of these compounds has been minimal. Hence efficient synthetic routes to this potentially useful natural products are needed. We herein report the first total syntheses of phenethyl glycosides **3** and **4** and a new synthetic method to get phenethyl glycoside **2** from inexpensive materials also has been developed.

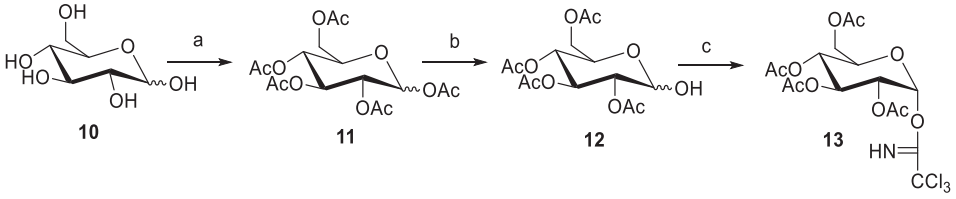
2. Results and discussion

As shown in Scheme 1, the synthesis of compound **2** began with readily available 4-hydroxyphenethyl alcohol **5**. Using the known method [13], compound **5** was bromized to generate compound **6** in 89% yield. The aryl bromide of **6** was displaced by methoxide in the presence of CuBr to obtain **7**. Then acetyl protection was used for the aromatic hydroxy group of **7**. Acetic anhydride was gradually added to a solution of **7** and aqueous NaOH for 45 min with the pH maintained at 7–8 to obtain compound **8** in good yield (78%) as the phenol hydroxyl group of reactant **7** could be ionized in the weak alkali reaction medium, but the alcohol hydroxyl could not.

On the other hand, rhamnose donor 2,3,4,6-tetra-*O*-acetyl-β-$_D$-glucopyranosyl trichloroacetimidate **13** was prepared from $_D$-glucose in three steps according to a literature method (Scheme 2, 62% overall yield) [14]. Phenylethanol **8** was glycosylated with rhamnose donor **13** in the presence of a catalytic amount of trimethylsilyl trifluoromethane sulfonate (TMSOTf) at −78 °C to give the β-linked monosaccharide derivative **9** as the major product in 85% yield. Removal of all five acetyl groups from compound **9** gave natural product **2** in quantity (Scheme 1).



Scheme 1. Synthetic route of compound **2**. Reagent and conditions: (a) NaBr, Oxone, acetone, H_2O, 0 °C, 1.5 h; (b) CuBr, CH_3ONa, DMF, 90 °C, 3 h; (c) acetic anhydride, NaOH, H_2O, 0–10 °C, 40 min; (d) compound 13, 4 Å molecular sieves, TMSOTf, −78 °C to 0 °C, 30 min; (e) CH_3ONa, CH_3OH, Amberlite IR 120, room temperature, 1.5 h.

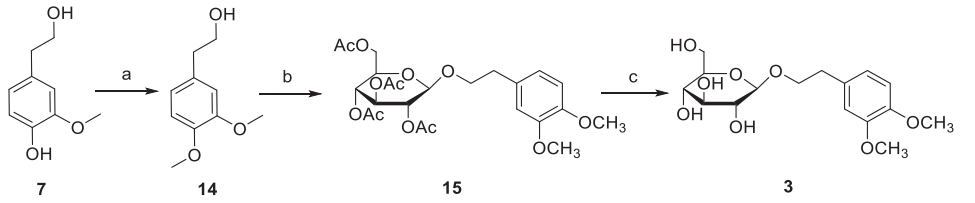


Scheme 2. Synthetic route of compound **13**. Reagent and conditions: (a) sodium acetate, acetic anhydride, 90 °C, 4 h; (b) hydrazine acetate, DMF, 50 °C, 2 h; (c) trichloroacetonitrile, DBU, CH_2Cl_2, room temperature, 2 h.

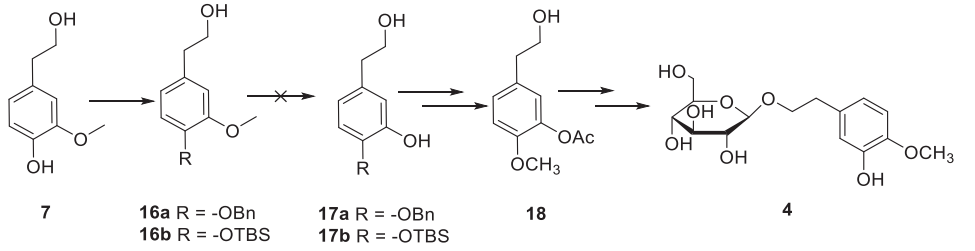
In 2013, Zheng and Guo et al. had reported a similar route to get phenethyl glycoside **2** [11]. In their strategy, benzyl group was used to protect phenol hydroxyl of compound **7**. The product was glycosylated with rhamnose donor acetyl-1-bromoglucose under Koenigs–Knorr conditions. Then acetyl and benzyl protection groups were removed by CH_3ONa/CH_3OH and Pd/C systems in two steps, respectively. Compared to their work, we represent a shorter and more convenient approach to obtain phenethyl glycoside **2**. As shown in Scheme 3, natural product **3** was readily obtained *via* a similar three-step sequence including methylation, glycosylation, and deprotection from compound **6**.

In an effort to promote the application of the above procedure, we sought to exploit similar ways to get phenethyl glycoside **4** (Scheme 4). But to our surprise, key intermediate **17** (**17a** or **17b**) could not be got from protected phenyl ethanol **16** (**16a** or **16b**) under various conditions.

So we resorted to another route for phenethyl glycoside **4**. Our new synthetic route started from commercially available phenylpropionic acid **19**. Treatment of **19** with $SOCl_2$ in CH_3OH yielded successfully methyl phenylacetate **20** in 84% yield. Then benzyl protection was taken to protect the aromatic hydroxy group of **20** to generate **21**. Compound **21** was reduced with $LiAlH_4$ (3 equiv.) to afford the corresponding alcohol **22** in 80% yield. Afterward, compound **23** was obtained by Schmidt's trichloroacetimidate procedure.



Scheme 3. Synthetic route of compound **3**. Reagent and conditions: (a) NaH, CH_3I, DMF, room temperature, 10 min (b) compound **13**, 4 Å molecular sieves, TMSOTf, −78 °C to 0 °C, 30 min; (c) CH_3ONa, CH_3OH, Amberlite IR 120, room temperature, 1.5 h.



Scheme 4. Design of initial attempt to prepare compound **4**.

In the last two steps, benzyl and acetyl protection groups of **23** were removed by Pd/C and CH_3ONa/CH_3OH systems to get natural product **4** (Scheme 5).

In summary, the first total syntheses of the naturally occurring and biologically interesting phenethyl glycosides **3** and **4** have been achieved. A new synthetic method to get 4-hydroxy-3-methoxyphenethyl β-$_D$-glucopyranoside (**2**) was also developed from inexpensive commercially available materials. All reaction steps were carried out by conventional reagents. The syntheses solve the problems of availabilities of the phenethyl glycosides for potential biomedical applications, as they are also excellent starting materials for the synthesis of other potential bioactive molecules.

3. Experimental

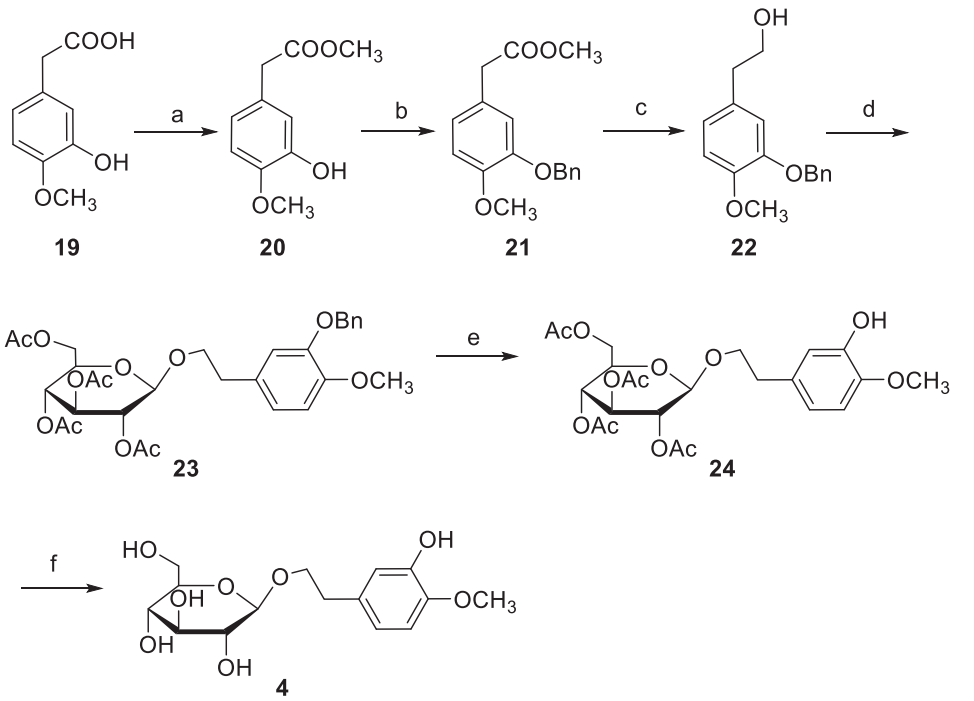
3.1. General experimental procedures

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. ^1H and ^{13}C NMR spectra were recorded on Brüker Avance 600 (Brüker Co., Fallanden, Switzerland) instrument (using tetramethylsilane as the internal standard). HR–MS were obtained on a Brüker Apex II mass spectrometer (Brüker Co., Bremen, Germany). The solvents were analytical grade and newly distilled before usage.

3.2. General procedures for the synthetic compounds

3.2.1. Synthesis of 2-bromo-4-(2-hydroxyethyl)phenol (6)

To a solution of hydroxyphenethyl alcohol **5** (13.8 g, 0.1 mol) in acetone (150 ml), was added NaBr (12.3 g, 12 mmol). Then a solution of Oxone in water (10 ml) was added at 0 °C in a period of 15 min. The reaction mixture was kept at 0 °C and stirred for



Scheme 5. Synthetic route of compound **4**. Reagent and conditions: (a) dichlorosulfoxide, CH_3OH, 0 °C, 6 h (b) K_2CO_3, BnBr, acetone, 60 °C, 4 h; (c) $LiAlH_4$, THF, 0 °C, 3 h; (d) compound **13**, 4 Å molecular sieves, TMSOTf, −78 °C to 0 °C, 30 min; (e) 10% Pd/C, H_2, THF, CH_3OH, room temperature, 24 h; (f) CH_3ONa, CH_3OH, Amberlite IR 120, room temperature, 1.5 h.

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 **6** as crystals (19.4 g, 89% yield), m.p. 88–90 °C. {lit. [15] m.p. 91–93 °C}. ^{1}H NMR (600 MHz, $CDCl_3$) *δ:* 7.33 (d, *J* = 2.1 Hz, 1H), 7.07 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.95 (d, *J* = 8.3 Hz, 1H), 5.44 (s, 1H, –OH), 3.81 (dd, *J* = 12.3, 6.5 Hz, 2H), 2.77 (t, *J* = 6.5 Hz, 2H); ^{13}C NMR (150 MHz, CD_3OD) *δ:* 152.6, 133.4, 132.3, 129.6, 116.6, 109.6, 62.66, 38.1.

3.2.2. Synthesis of 4-(2-hydroxyethyl)-2-methoxyphenyl (7)

To a solution of compound **6** (15 g, 69.1 mmol) in DMF (20 ml) was added CuBr (1.0 g, 6.9 mmol) and 1.5 ml solution of 25% CH_3ONa/CH_3OH. The reaction mixture was heated at 90 °C and kept under magnetic stirring for 3 h, quenched with 2 M HCl, and diluted with H_2O. The solution was extracted with ethyl acetate (3 × 150 ml), and the organic layers were collected, washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by flash chromatography using ethyl acetate/petroleum ether 1:4 as eluent to give pure **7** 12.6 g, yield 87.6%, m.p. 55–58 °C. {lit. [16] m.p. 62–65 °C}. ^{1}H NMR (600 MHz, $CDCl_3$) *δ:* 6.84 (d, *J* = 7.8 Hz, 1H), 6.71–6.70 (m, 2H), 5.64 (s, 1H, –OH), 3.86 (s, 3H), 3.81 (t, *J* = 6.5 Hz, 2H), 2.78 (t, *J* = 6.5 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) *δ:* 146.7, 144.3, 130.3, 121.7, 114.6, 111.7, 63.9, 55.9, 38.8.

3.2.3. Synthesis of 4-(2-hydroxyethyl)-2-methoxyphenol acetate (8)

Compound **7** (2.76 g, 20 mmol) was added to a stirred solution of 6 ml 6 M NaOH. Then the temperature of the system was decreased to 0 °C, and acetic anhydride (2.45 g, 24 mmol) was added slowly over 40 min under vigorously stirring with the pH maintained at 7–8. The addition was exothermic, and the temperature was no more than 10 °C. The solution was extracted three times with EtOAc (3 × 20 ml), and the combined organic solutions were washed with brine, dried over Na_2SO_4, and then concentrated *in vacuo* to get a colorless oil compound **8** 2.15 g (yield 78%) which is pure enough for the next step. ^{1}H NMR (600 MHz, $CDCl_3$) *δ:* 6.95 (d, $J = 8.0$ Hz, 1H), 6.82 (d, $J = 1.9$ Hz, 1H), 6.79 (dd, $J = 8.0$, 1.9 Hz, 1H), 3.86–3.83 (m, 2H), 2.84 (t, $J = 6.5$ Hz, 2H), 2.83 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) *δ:* 169.6, 150.9, 138.2, 137.9, 122.7, 121.2, 113.3, 63.5, 55.9, 39.1, 20.8.

3.2.4. Synthesis of β-$_D$-glucose pentaacetate (11)

A mixture of dextrose **10** (5.0 g, 27.7 mmol) and sodium acetate (6.83 g, 83.3 mmol) was dissolved in acetic anhydride (43 ml, 0.46 mol). The reaction mixture was refluxed for 4 h at 90 °C. After the reaction time, the reaction mixture was cooled to r.t. and then poured into the beaker containing crushed ice (250 ml) under stirring conditions. The penta-acetate was precipitated. The precipitation was filtered and washed with ice-cold water until the odor of the acetic acid disappeared. The crude product was purified by recrystalization from MeOH to afford the title compound **11** (9.96 g, 92%) as a white crystalline solid, m.p. 130–135 °C. {lit. [17] m.p. 130–135 °C}.

3.2.5. Synthesis of 2,3,4,6-tetra-O-acetyl-$_D$-glucopyranose (12)

Hydrazine acetate (2.0 g, 22.6 mmol) was added to a solution of glucopyranoside **11** (8 g, 10.3 mmol) in N,N-dimethylformamide (DMF, 60 mL) at 50 °C and the reaction was stirred for 2 h under N_2. Then the mixture was diluted with EtOAc, washed with aqueous 5% NaCl and water, dried over anhydrous Na_2SO_4, and concentrated to give yellow oil. This crude oil was subjected to silica gel column chromatography. The residue was purified by flash chromatography using ethyl acetate/hexane 1:2 as eluent to give **12** (92%, 6.5 g) as a colorless oil.

3.2.6. Synthesis of O-(2,3,4,6-tetra-O-acetyl-α-$_D$-glucopyranosyl)trichloroacetimidate (13)

Compound **12** (7 g, 20 mmol) was treated with trichloroacetonitrile (28.4 g, 200 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.5 ml, 20 mmol) in anhydrous CH_2Cl_2 (150 ml) and stirred for 2 h at r.t. After 2 h, the reaction mixture was concentrated under reduced pressure and purified by silica gel column chromatography. The required product was eluted in petroleum ether: EtOAc (4:1, v/v) solvent mixture, and **13** was isolated as an yellow oil (7.3 g, 73%), $[\alpha]^{20}_D$ +60.2 (c 1.5, $CHCl_3$). {lit. [18] $[\alpha]^{20}_D$ +67.2 (c 1.0, $CHCl_3$)}. ^{1}H NMR (600 MHz, $CDCl_3$) *δ:* 8.66 (s, 1H), 6.47 (d, $J = 3.7$ Hz, 1H), 5.47 (t, $J = 9.9$ Hz, 1H), 5.13–5.07 (m, 1H), 5.05 (dd, $J = 10.2$, 3.7 Hz, 1H), 4.19 (dd, $J = 12.5$, 4.2 Hz, 1H), 4.13 (ddd, $J = 10.3$, 4.2, 2.2 Hz, 1H), 4.02–4.07 (m, 1H), 1.99 (s, 3H), 1.97 (s, 3H), 1.95 (s, 3H), 1.93 (s, 3H).

3.2.7. Synthesis of (2R,3R,4S,5R,6R)-2-(4-acetoxy-3-methoxyphenethoxy)-6-(acetoxymethyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (9)

A mixture of **8** (0.336 g, 1.6 mmol), **13** (1.47 g, 3 mmol), and 4 Å molecular sieves (1.0 g) was added to dry CH_2Cl_2 (30 ml) under argon atmosphere at −78 °C. The mixture was stirred for 30 min and TMSOTf (cat., 10 μl) 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 the addition of Et_3N and concentrated. The crude product was purified by column chromatography (petroleum ether: EtOAc 1:2 V/V) to give **9** (0.73 g, 85%) as a colorless oil, $[\alpha]^{20}_D$ −40.2 (c 1.3, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) *δ:* 6.89 (d, *J* = 8.0 Hz, 1H), 6.77 (d, *J* = 1.8 Hz, 1H), 6.72 (dd, *J* = 8.0, 1.8 Hz, 1H), 5.14 (t, *J* = 9.7 Hz, 1H), 5.05 (t, *J* = 9.7 Hz, 1H), 4.96 (dd, *J* = 9.7, 8.0 Hz, 1H), 4.45 (d, *J* = 8.0 Hz, 1H), 4.24 (dd, *J* = 12.3, 4.7 Hz, 1H), 4.14–4.09 (m, 2H), 3.80 (s, 3H), 3.68–3.63 (m, 1H), 3.63–3.59 (m, 1H), 2.85–2.83(m, 2H), 2.26 (s, 3H), 2.06 (s, 3H), 1.99 (s, 3H), 1.96 (s, 3H), 1.85 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) *δ:* 171.2, 170.8, 169.7, 169.2, 169.1, 150.8, 138.2, 137.8, 122.6, 121.1, 113.4, 96.8, 72.9, 69.8, 68.3, 66.8, 64.2, 63.2, 55.9, 36.1, 20.9, 20.8, 20.8, 20.7, 20.6.

3.2.8. Synthesis of (2R,3R,4S,5S,6R)-2-(4-hydroxy-3-methoxyphenethoxy)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (2)

To a solution of **9** (0.73 g,1.35 mmol) in CH_3OH (20 ml) was added the solution of CH_3ONa (150 mg, 3 mmol) at 0 °C. The mixture was stirred at room temperature for 1.5 h. After the reaction was completed (detected by TLC), Amberlite IR 120 (3 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 white powder compound **2** in 90% yield, m.p. 150–155 °C, $[\alpha]^{20}_D$ −20.2 (c 1.0, CH_3OH). {lit. [10] $[\alpha]^{25}_D$ −12.5 (c 0.13, CH_3OH)}. ^{1}H NMR (600 MHz, CD_3OD) *δ:* 6.85 (d, *J* = 1.8 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 6.67 (dd, *J* = 8.0, 1.8 Hz, 1H), 4.31 (d, *J* = 7.8 Hz, 1H), 4.02–4.07 (m, 1H), 3.87 (dd, *J* = 11.9, 1.7 Hz, 1H), 3.83 (s, 3H), 3.80–3.60 (m, 2H), 3.42–3.15 (m, 4H), 2.92–2.78 (m, 2H); ^{13}C NMR (150 MHz, CD_3OD) *δ:* 148.8, 145.9, 131.6, 122.5, 116.1, 113.8, 104.3, 78.1, 77.9, 75.1, 72.0, 71.7, 62.8, 56.5, 36.9. HR-ESI-MS: *m/z* 331.1390 $[M+H]^+$ (calcd for $C_{15}H_{23}O_8$, 331.1387).

3.2.9. Synthesis of 2-(3,4-dimethoxyphenyl)ethan-1-ol (14)

To a mixture of **7** (1.68 g, 10 mmol), NaH (0.24 g, 10 mmol) in 20 ml dry DMF, a solution of CH_3I (2.16 g, 15 mmol) in 10 ml DMF was added in 20 min. Then the stirring was continued for further 10 min. The reaction was quenched by water (20 ml), extracted with ethyl acetate (3 × 50 ml), and the organic layers were collected, washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by flash chromatography using ethyl acetate/petroleum ether 1:4 as eluent, to give pure **14** (1.70 g, 93%) as a colorless oil. ^{1}H NMR (600 MHz, CD_3OD) *δ:* 6.80–6.77 (m, 2H), 6.68–6.66 (m, 1H), 3.69 (s, 3H), 3.66 (s, 3H), 3.55 (t, *J* = 7.3 Hz, 2H), 2.62 (t, *J* = 7.3 Hz, 2H); ^{13}C NMR (150 MHz, CD_3OD) *δ:* 149.0, 147.6, 132.5, 121.2, 113.3, 112.3, 62.9, 56.0, 55.9, 39.2.

3.2.10. Synthesis of (2R,3R,4S,5R,6R)-2-(acetoxymethyl)-6-(3,4-dimethoxyphenethoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (15)

The procedure was the same as compound **8** in Section 3.2.7 from compound **14** to afford a light yellow solid **15** in 78% yield, m.p. 100–103 °C, $[\alpha]^{20}_{D}$ −33.0 (c 0.8, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) *δ:* 6.76–6.74 (m, 1H), 6.70–6.68 (m, 2H), 5.14 (t, *J* = 9.5 Hz, 1H), 5.05 (t, *J* = 8.0 Hz, 1H), 4.96 (dd, *J* = 9.5, 8.0 Hz, 1H), 4.45 (d, *J* = 8.0 Hz, 1H), 4.23 (dd, *J* = 12.3, 4.7 Hz, 1H), 4.12–4.04 (m, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 3.65 (ddd, *J* = 10.0, 4.6, 2.4 Hz, 1H), 3.60 (dt, *J* = 9.5, 7.3 Hz, 1H), 2.79 (t, *J* = 6.8 Hz, 2H), 2.05 (s, 3H), 1.98 (s, 3H), 1.96 (s, 3H), 1.85 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) *δ:* 170.8, 170.4, 169.5, 169.2, 150.8, 138.2, 137.5, 122.5, 121.1 113.5, 100.9, 72.8, 71.9, 71.1, 70.6, 68.5, 62.0, 55.9, 55.9, 35.9, 20.8, 20.7, 20.7, 20.5.

3.2.11. Synthesis of (2R,3R,4S,5S,6R)-2-(3,4-dimethoxyphenethoxy)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (3)

The procedure was the same as compound **2** in Section 3.2.8 from compound **15** to afford a light yellow oil **3** in 90% yield, $[\alpha]^{20}_{D}$ −28.2 (c 1.0, CH_3OH). {lit. [7] $[\alpha]_D$ −20.1 (CH_3OH)} ^{1}H NMR (600 MHz, CD_3OD) *δ:* 6.85 (d, *J* = 1.7 Hz, 1H), 6.79 (d, *J* = 8.2 Hz, 1H), 6.74 (dd, *J* = 8.2, 1.7 Hz, 1H), 4.29 (d, *J* = 7.8 Hz, 1H), 4.04 (dt, *J* = 9.4, 7.6 Hz, 1H), 3.85 (dd, *J* = 11.9, 1.8 Hz, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 3.72–3.63 (m, 2H), 3.38–3.19 (m, 4H), 2.85–2.82 (m, 2H); ^{13}C NMR (150 MHz, CD_3OD) *δ:* 148.9, 147.6, 131.7, 121.0, 112.7, 111.7, 103.0, 76.7, 76.5, 73.8, 70.5, 70.3, 61.5, 55.3, 55.2, 35.4. HR-ESI-MS: *m/z* 345.1541 $[M+H]^+$ (calcd for $C_{16}H_{25}O_8$, 345.1544).

3.2.12. Synthesis of methyl 2-(3-hydroxy-4-methoxyphenyl)acetate (20)

To a stirred solution of 3-(3-hydroxy-4-methoxyphenyl)propanoic acid **19** (5.0 g, 25.5 mmol) in 100 ml CH_3OH was added dichlorosulfoxide (5 ml) at 0 °C. After stirring for 6 h at 0 °C, the solution was diluted with ether (200 ml) and washed with water (100 ml). The aqueous layer was then further extracted with ether (2 × 50 ml), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide yellow oil **20** (4.8 g, 84%). ^{1}H NMR (600 MHz, $CDCl_3$) *δ:* 6.85–6.84 (m, 1H), 6.77–6.71 (m, 2H), 3.80 (s, 3H), 3.65 (s, 3H), 3.51 (s, 2H); ^{13}C NMR *δ:* 172.4, 145.9, 145.7, 127.1, 120.8, 115.7, 110.9, 55.9, 52.0, 40.5.

3.2.13. Synthesis of methyl 2-(3-benzyloxy-4-methoxyphenyl)acetate (21)

To a stirred solution of compound **20** (1.5 g, 7.14 mmol) and K_2CO_3 (3.41 g, 24.7 mmol) in 20 ml acetone was added BnBr (1.41 ml, 11.7 mmol) dropwise at room temperature. After stirring for 4 h at 60 °C, the solution was diluted with CH_2Cl_2 (50 ml) and washed with water (50 ml). The aqueous layer was then further extracted with CH_2Cl_2 (2 × 50 ml), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to get white solid compound **21** (2.3 g, 81%), m.p. 58–61 °C. ^{1}H NMR (600 MHz, $CDCl_3$) *δ:* 7.45–7.43 (m, 2H), 7.38–7.34 (m, 2H), 7.31–7.29 (m, 1H), 6.85–6.83 (m, 3H), 5.13 (s, 2H), 3.86 (s, 3H), 3.64 (s, 3H), 3.51 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) *δ:* 172.2, 148.9, 148.2, 137.1, 128.5, 127.8, 127.4, 126.4, 122.0, 115.1, 111.9, 71.0, 56.1, 52.0, 40.7.

3.2.14. Synthesis of 2-(3-benzyloxy-4-methoxyphenyl)ethan-1-ol (22)

A mixture of **21** (1.5 g, 5 mmol) and $LiAlH_4$ (0.57 g, 15 mmol) was added to dry THF (30 ml) under argon atmosphere at 0 °C. The mixture was stirred for 3 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 compound **22** (1.03 g, 80% yield) as an colorless solid, m.p.70–72 °C. {lit. [19] m.p. 80–80.5 °C}. ^{1}H NMR (600 MHz, $CDCl_3$) *δ:* 7.43 (d, $J = 7.5$ Hz, 2H), 7.35 (t, $J = 7.5$ Hz, 2H), 7.30–7.29 (m, 1H), 6.84 (d, $J = 8.0$ Hz, 1H), 6.77–6.76 (m, 2H), 5.14 (s, 2H), 3.86 (s, 3H), 3.76 (q, $J = 6.3$ Hz, 2H), 2.74 (t, $J = 6.3$ Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) *δ:* 148.5, 148.2, 137.2, 130.9, 128.6, 127.9, 127.5, 121.7, 115.2, 112.1, 71.1, 63.8, 56.2, 38.7.

3.2.15. Synthesis of (2R,3R,4S,5R,6R)-2-(acetoxymethyl)-6-[3-(benzyloxy)-4-methoxyphenethoxy]tetrahydro-2H-pyran-3,4,5-triyl triacetate (23)

Compound **23** was get with a similar approach to compound **8** (yield 90%), m.p. 135–137 °C, $[\alpha]^{20}_D$ −14.8 (c 0.7, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) *δ:* 7.44 (d, $J = 7.4$ Hz, 2H), 7.35 (t, $J = 7.4$ Hz, 2H), 7.29 (d, $J = 7.4$ Hz, 1H), 6.79 (d, $J = 8.0$ Hz, 1H), 6.75–6.70 (m, 2H), 5.19–5.04 (m, 4H), 4.97 (dd, $J = 9.6$, 8.0 Hz, 1H), 4.42 (d, $J = 8.0$ Hz, 1H), 4.25 (dd, $J = 12.3$, 4.6 Hz, 1H), 4.11 (dd, $J = 12.2$, 2.2 Hz, 1H), 4.04 (dt, $J = 9.4$, 6.3 Hz, 1H), 3.84 (s, 3H), 3.65 (ddd, $J = 10.0$, 4.6, 2.2 Hz, 1H), 3.56 (dt, $J = 9.3$, 7.4 Hz, 1H), 2.76 (t, $J = 6.5$ Hz, 2H), 2.06 (s, 3H), 2.04 (s, 3H), 1.98 (s, 3H), 1.87 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) *δ:* 170.8, 170.4, 169.5, 169.4, 148.3, 148.0, 137.3, 131.0, 128.6, 127.9, 127.5, 121.6, 115.2, 111.9, 100.9, 72.8, 71.9, 71.1, 71.0 (2 × C), 68.5, 62.0, 56.2, 35.5, 20.9, 20.7, 20.7, 20.6.

3.2.16. Synthesis of (2R,3R,4S,5R,6R)-2-(acetoxymethyl)-6-(3-hydroxy-4-methoxyphenethoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (24)

A suspension of **23** (100 mg, 0.17 mmol) and palladium (20 mg, 10 wt.% on activated carbon) in THF (3 ml) and CH_3OH (30 ml) was stirred at room temperature under hydrogen gas atmosphere for 24 h. After the reaction was completed, the mixture was filtered through a pad of Celite. The filtrate was then concentrated *in vacuo* to get compound **24** (80 mg, 90%) as a colorless oil, $[\alpha]^{20}_D$ −28.8 (c 0.1, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) *δ*: 6.75–6.73 (m, 2H), 6.64 (dd, $J = 8.1$, 2.1 Hz, 1H), 5.16 (t, $J = 9.5$ Hz, 1H), 5.13–5.02 (m, 1H), 4.98 (dd, $J = 9.5$, 8.0 Hz, 1H), 4.46 (d, $J = 8.0$ Hz, 1H), 4.24 (dd, $J = 12.3$, 4.7 Hz, 1H), 4.12 (dd, $J = 12.3$, 2.4 Hz, 1H), 4.08–4.04 (m, 1H), 3.84 (s, 3H), 3.66 (ddd, $J = 10.0$, 4.7, 2.4 Hz, 1H), 3.61 (dt, $J = 9.6$, 7.3 Hz, 1H), 2.89–2.63 (m, 2H), 2.07 (s, 3H), 2.00 (s, 3H), 1.98 (s, 3H), 1.94 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) *δ:* 170.8, 170.4, 169.5, 169.5, 145.5, 145.2, 131.8, 120.5, 115.2, 110.7, 100.8, 72.9, 71.9, 71.2, 70.9, 68.5, 62.0, 56.0, 35.4, 20.8, 20.7, 20.7, 20.6.

3.2.17. Synthesis of (2R,3R,4S,5S,6R)-2-(3-hydroxy-4-methoxyphenethoxy)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (4)

Compound **4** was obtained with a similar approach to compound **2** (yield 91%) as a colourless oil, $[\alpha]^{20}_D$ −17.3 (c 0.07, CH_3OH), {lit. [20] $[\alpha]^{31}_D$ −12.9 (0.33, CH_3OH)}.

^{1}H NMR (600 MHz, CD_3OD) *δ:* 6.83 (d, $J = 8.2$ Hz, 1H), 6.75 (d, $J = 2.1$ Hz, 1H), 6.70 (dd, $J = 8.2$, 2.1 Hz, 1H), 4.31 (d, $J = 7.8$ Hz, 1H), 4.08–4.04 (m, 1H), 3.88 (dd, $J = 11.9$, 2.1 Hz, 1H), 3.83 (s, 3H), 3.75–3.66 (m, 2H), 3.39–3.36 (m, 1H), 3.33–3.32 (m, 1H), 3.30–3.27 (m, 1H), 3.21 (dd, $J = 9.1$, 7.9 Hz, 1H), 2.88–2.77 (m, 2H); ^{13}C NMR (150 MHz, CD_3OD) *δ:* 146.1, 146.0, 131.5, 119.8, 115.7, 111.5, 103.0, 76.7, 76.5, 73.7, 70.5, 70.2, 61.3, 55.1, 35.2. HR-ESI-MS: *m/z* 331.1395 $[M + H]^+$ (calcd for $C_{15}H_{23}O_8$, 331.1387).

Disclosure statement

No potential conflict of interest was reported by the author(s).

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