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Carbohydrate Research 342 (2007) 2309–2315
Carbohydrate RESEARCH

Note

# Total synthesis of phenylpropanoid glycosides, grayanoside A and syringalide B, through a common intermediate☆

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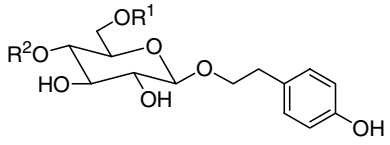
Received 18 April 2007; received in revised form 15 June 2007; accepted 19 June 2007
Available online 28 June 2007

**Abstract**—Phenylpropanoid glycosides are known as bioactive natural products. Two of them, grayanoside A (**1**) and syringalide B (**2**), were synthesized through a common intermediate, using benzyl as temporary protecting group following a shorter route.


*Keywords:* Phenylpropanoid glycosides; Grayanoside A; Syringalide B; Synthesis; Monosaccharide; Feruloyl

Phenylpropanoid glycosides are naturally occurring glycosides acylated with a substituted cinnamoyl residue having a substituted phenethyl group as aglycon.[1] Most of them possess biological activities such as antiviral, antimicrobial, hepato-protective, antitumour, antifungal, improved immune function and sedative effects.[1–8] Very recently, Lin and co-workers suggested that the inhibition of reactive oxygen species (ROS) production, possibly through modulation of NADPH oxidase (NOX) activity and/or the radical scavenging effect, as well as β2 integrin expression in leucocytes, indicated that the phenylpropanoid glycosides had the potential to serve as anti-inflammatory agents during oxidative stress.[9] More than 100 phenylpropanoid glycosides have already been isolated and characterized by spectral and chemical conversions. However, the low content of phenylpropanoid glycosides in most of the plant species has limited further investigation of their activities. Thus, it becomes important to provide a synthetic route to these phenylpropanoid glycosides.

Grayanoside A (**1**, Fig. 1), a monosaccharide phenylpropanoid glycoside, was isolated from the bark of *Pranus grayana*[10] and syringalide B (**2**, Fig. 1), an isomer of grayanoside A, was isolated from *Syringa reticulata* leaf.[11] Cai and co-workers have reported[12,13] the syntheses of these two phenylpropanoid glycosides following two different routes and through different intermediates. Here we wish to report the syntheses of both the phenylpropanoid glycosides through a common intermediate, thereby reducing the number of steps.




**1:** $R^1$= feruloyl, $R^2$= H; grayanoside A
**2:** $R^1$= H, $R^2$= feruloyl; syringalide B

**Figure 1.** Structures of grayanoside A and syrigalide B.

Protecting group manipulation plays an important role in organic synthesis. After considering the structures of both the phenylpropanoid glycosides, it appeared that the benzyl group could possibly impart the necessary assistance to obtain two compounds through a common, late-stage intermediate, although selective removal of benzyl groups without affecting the double bond was a challenge. A literature search provided the confidence that the acteoside had been synthesized[14] using benzyl protection and bearing a similar kind of

☆ DRL Publication No. 608.

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doi:10.1016/j.carres.2007.06.022

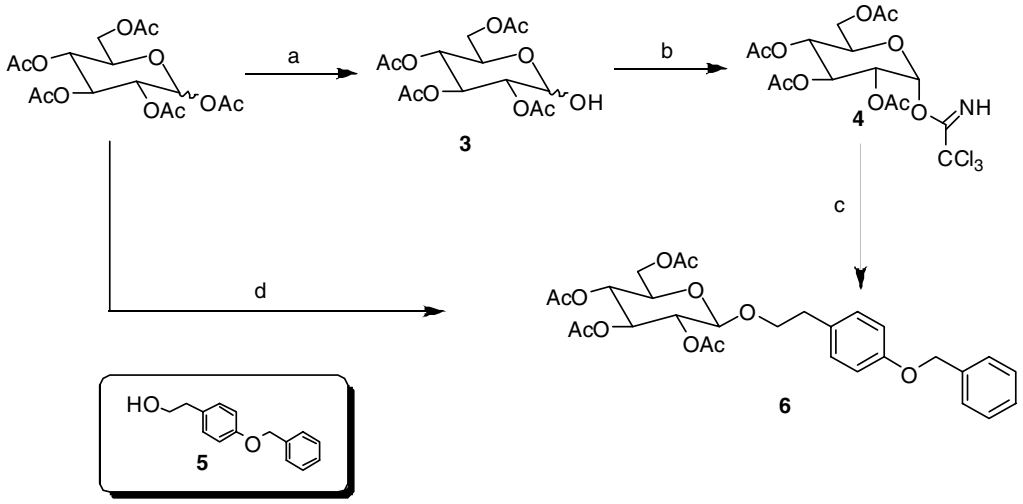
cinnamoyl residue. The literature survey also indicated that Cai and co-workers[12] already used allyl or allyloxycarbonyl groups for the synthesis of grayanoside A. This was another reason to choose benzyl as protective group. After we started the work, there was a report[13] on the synthesis of syringalide B, the other isomer, following a similar allyl protective group strategy.

Our strategy for the total syntheses of the two isomers **1** and **2** involved a convergent route from phenethyl glycoside **6**, obtained from glucose pentaacetate[15] and the phenethyl derivative **5** (Scheme 1). Initially we wanted to follow Schmidt's trichloroacetimidate procedure to obtain phenethyl glycoside **6**. Accordingly, 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose (**3**) was obtained from glucose pentaacetate[15] using hydrazine acetate.[16] Compound **3** was then converted to the trichloroacetimidate derivative **4** following literature procedure.[17] TMSOTf-promoted[18] glycosylation of **4** using 2-(4-benzyloxyphenyl)ethyl alcohol afforded phenethyl glycoside **6** in only 34% yield. The overall yield seemed to be unsatisfactory, and we turned our interest to a single-step procedure. Thus, glucose pentaacetate was reacted with boron trifluoride etherate to afford phenethyl glycoside **6** in 60% yield (see Scheme 1).

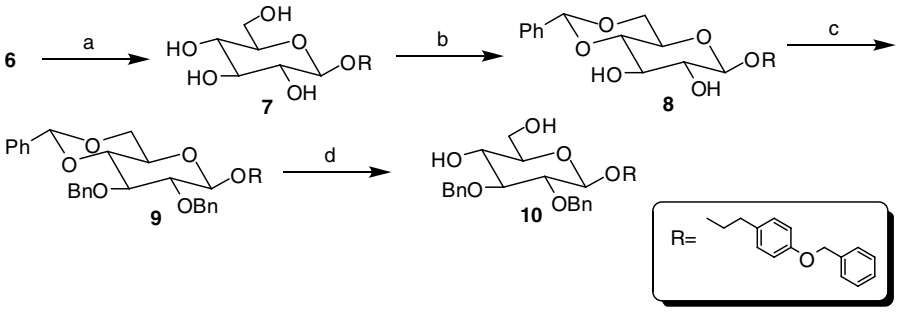
Compound **6** was then treated with sodium methoxide in methanol to remove the acetyl groups, followed by benzylidination using α,α-dimethoxytoluene[19] in the presence of a catalytic amount of *p*-toluenesulfonic acid (Scheme 2) to afford benzylidene derivative **8** in 95% yield over two steps. Compound **8** was then converted to its dibenzyl derivative **9** (90% yield) using benzyl bromide in DMF in the presence of sodium hydride, which on hydrolysis using aqueous acetic acid furnished crucial intermediate **10** in 82% yield.

In the next step, protected ferulic acid derivative **13** was prepared starting from 4-hydroxy-3-methoxy cinnamic acid (**11**) following a reported procedure[20] (Scheme 3).

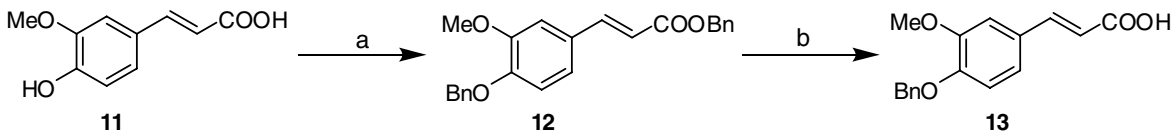
The ferulic acid derivative **13** was then reacted with the synthesized glycoside **10** using 3-ethyl-1-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI)[21] in the presence of 4-(dimethylamino)pyridine (DMAP) in dichloromethane where both 6-*O*-acyl as well as 4-*O*-acyl derivatives **14** and **15**, respectively, were obtained




**Scheme 1.** Reagents and conditions: (a) Hydrazine acetate, DMF, 60 °C, 40 min, 93%; (b) $CCl_3CN$, DBU, $CH_2Cl_2$, rt, 30 min, 76%; (c) 5, TMSOTf, $Et_2O$, rt, 1 h, 34%; (d) 5, $CH_2Cl_2$, $BF_3{\cdot}OEt_2$, rt, 6 h, 60%.




**Scheme 2.** Reagents and conditions: (a) NaOMe, MeOH, rt, 4 h, quant.; (b) α,α-dimethoxytoluene, *p*-TsOH, DMF, rt, 24 h, 95%; (c) BnBr, NaH, DMF, rt, 20 h, 90%; (d) 80% AcOH, 80 °C, 90 min, 82%.

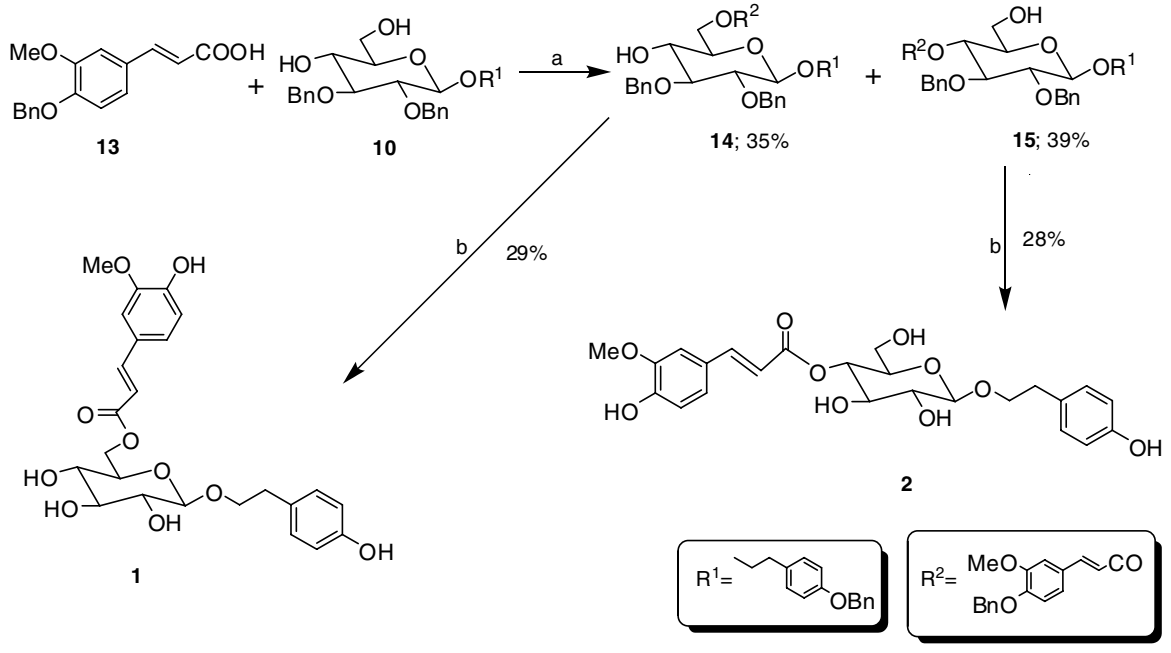



**Scheme 3.** Reagents and conditions: (a) BnBr, $K_2CO_3$, DMF, rt, overnight, 96%; (b) LiOH, THF–MeOH–$H_2O$, rt, 40 h, 92%.

in 35% and 39% yields as shown in Scheme 4. The reason for obtaining a marginally higher yield for the 4-*O*-acyl derivative is not clear to us, although before assigning the structures through 1D and 2D NMR experiments, we assumed the opposite result, since a primary hydroxyl group generally shows greater reactivity. These two compounds were easily separated by normal silica gel column chromatography method. The $^1H$, $^1H$–$^1H$ COSY and $^1H$–$^{13}C$ HSQC NMR experiments were used to assign the protons and carbons in compounds **14** and **15**. The protons H-4, H-5, H-6a and H-6b were assigned at $\delta$ 3.52 ($\delta$ 70.2), $\delta$ 3.46 (83.9), $\delta$ 4.38 and $\delta$ 4.58 ($\delta$ 63.3), respectively; the figures in the parentheses being the position of corresponding C. To confirm the position of substitution of the cinnamoyl group on the sugar moiety, the HMBC experiment was performed, the results of which are shown in Figure 2. The carbon chemical shift of the cinnamoyl carbonyl was easily assigned at $\delta$ 168.2 from its long-range heteronuclear correlations with the olefinic protons at $\delta$ 7.63 and $\delta$ 6.34. Further the cinnamoyl carbonyl carbon at $\delta$ 168.2 showed long-range heteronuclear correlations with protons at $\delta$ 4.38 and $\delta$ 4.58, which were assigned for H-6a and H-6b on the sugar moiety. This shows that the substitution (cinnamoyl group) is at C-6 in **14**.

The protons of H-4, H-5, H-6a and H-6b were assigned at $\delta$ 5.06 ($\delta$ 70.8), $\delta$ 3.40 ($\delta$ 74.6), $\delta$ 3.61 and $\delta$ 3.70 ($\delta$ 61.7), respectively. Through the same HMBC experiment, the carbon chemical shift of the cinnamoyl carbonyl was assigned at $\delta$ 167.0 from its long-range heteronuclear correlations with the olefinic protons at $\delta$ 7.60 and $\delta$ 6.15. Further the cinnamoyl carbonyl carbon at $\delta$ 167.0 showed long-range heteronuclear correlations with the proton at $\delta$ 5.06, which was assigned for H-4 on the sugar moiety. This shows that the substitution (cinnamoyl group) is at C-4 in **15**.

The last step was the debenzylation of compounds **14** and **15**. We first tried the ammonium formate–10% Pd/C transfer hydrogenolysis method.[22] To our surprise, the analysis indicated that the double bond got reduced along with three of the four benzyl groups. The $BCl_3$ method[23] afforded only 10% conversion, and the isolated product contained three benzyl protections intact. When we tried the $FeCl_3$ method,[24] a very highly polar product formed that was not characterized. Finally the desired products were obtained when we used 1,4-cyclohexadiene in the presence of Pd/C in a DMF–EtOH mixture, following a known protocol for the transfer hydrogenolysis.[14] It is pertinent to say that the yields of the reaction were poor mainly due to incomplete




**Scheme 4.** Reagents and conditions: (a) EDCI, DMAP, $CH_2Cl_2$, rt, 1 h; (b) 1,4-cyclohexadiene, 5% Pd/C, DMF–EtOH, rt, 10 h.

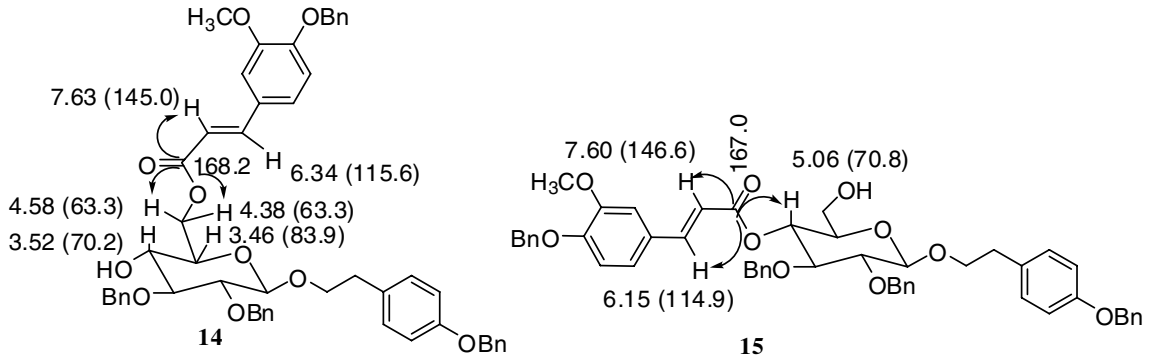



**Figure 2.** Structures and chemical shifts for **14** and **15**.

removal of benzyl protections. Even after several days, the reaction did not go for completion.

The advantage of this synthetic strategy is that both grayanoside A and syringalide B can be synthesized in reasonably good yields through a common intermediate through less number of reaction steps.

## 1. Experimental

### 1.1. General methods

The $^1$H NMR spectra were recorded with tetramethylsilane (TMS, $\delta$ 0.00) as the internal standard and calibration of $^{13}$C NMR spectra were done with residual solvent peaks on a Varian Gemini 200 or 400 MHz FT NMR spectrometer. Mass spectra were measured on Hewlett-Packard 5989A mass spectrometer [chemical ionization, (CI), 20 eV] or on a Perkin–Elmer Sciex model API 3000 [electrospray ionization, (ESI), capillary voltage between +5000 and −4500 V]. The HRMS studies were performed on a Waters LCT premier XE instrument. The FTIR spectra were recorded using a Perkin–Elmer 1650 fourier-transform infrared spectrophotometer. Optical rotations were measured using a JASCO DIP-370 polarimeter at room temperature (25 °C). Melting points were measured in glass capillary tubes on a digital melting point apparatus model No. Büchi-535 and were uncorrected. All the chromatography solvents were distilled before use. Silica gel (100–200 mesh, SRL, India) was used for column chromatography.

### 1.2. 2-(4-Benzyloxyphenyl)ethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (6)

To an ice cooled solution of glucose pentaacetate (1.0 g, 2.56 mmol) and 2-(4-benzyloxyphenyl)-1-ethanol (1.17 g, 5.13 mmol) in $CH_2Cl_2$ (10 mL) boron trifluoride etherate (0.64 mL) was added dropwise with stirring at room temperature. The mixture was stirred for 6 h and then was diluted with $CH_2Cl_2$ (50 mL). The organic phase was washed successively with water and brine, dried (anhyd $Na_2SO_4$) and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography using 35:65 EtOAc–petroleum ether to afford a colourless gummy mass of **6**: yield 0.86 g (60%); $R_f$ 0.32 (1:3 EtOAc–petroleum ether); $[\alpha]_D$ −1.8 (*c* 0.5, $CHCl_3$); IR (Neat): 2940, 1766, 1512, 1368, 1223, 1040 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.89 (s, 3H, Ac), 1.99 (s, 3H, Ac), 2.02 (s, 3H, Ac), 2.08 (s, 3H, Ac), 2.82 (t, 2H, *J* 6.4 Hz, $OCH_2$–C*H*$_2$-Ph), 3.60–3.78 (m, 2H, H-5 and OC*H*$_2$–$CH_2$-Ph), 4.05–4.09 (m, 1H, OC*H*$_2$–$CH_2$-Ph), 4.13 (dd, 1H, *J* 2.4 and 12.4 Hz, H-6a), 4.25 (dd, 1H, *J* 4.8 and 12.4 Hz, H-6b), 4.48 (d, 1H, *J* 8.0 Hz, H-1), 4.98 (t, 1H, *J* 8.8 Hz, H-2), 5.04 (s, 2H, OC*H*$_2$-Ph), 5.07 (t, 1H, *J* 9.6 Hz, H-4), 5.17 (t, 1H, *J* 9.4 Hz, H-3), 6.88 (d, 2H, *J* 8.8 Hz, Ph), 7.01 (d, 2H, *J* 8.4 Hz, Ph), 7.29–7.43 (m, 5H, Ph). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 20.6 ($2CH_3$), 20.7 ($2CH_3$), 35.0, 61.9, 68.5, 70.0, 70.9, 71.2, 71.8, 72.8, 100.8 (C-1), 114.8 (2C), 127.4 (2C), 127.9, 128.6 (2C), 129.9 (2C), 130.8, 137.1, 157.4, 169.3, 169.4, 170.3, 170.7. ESIMS: *m*/*z* 576.4 ($M^+$+18). HRMS *m*/*z*: calcd for $C_{29}H_{34}O_{11}Na$, 581.1999; found 581.1979. Anal. Calcd for $C_{29}H_{34}O_{11}$: C, 62.36; H, 6.13. Found: C, 62.05; H, 5.91.

### 1.3. 2-(4-Benzyloxyphenyl)ethyl β-D-glucopyranoside (7)

To a solution of compound **6** (0.95 g, 1.70 mmol) in MeOH (3.5 mL) was added 1 M NaOMe (0.19 mL), and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with MeOH and neutralized with Dowex-50W ($H^+$) resin. The reaction mixture was filtered through cotton, evaporated to dryness under reduced pressure, flashed with toluene and dried to afford **7** as a white solid: yield 0.65 g (quant); $R_f$ 0.2 (EtOAc); mp 96–98 °C; $[\alpha]_D$ +0.4 (*c* 0.5, MeOH); IR: 3264, 2913, 1659, 1512, 1250, 1105, 1028 cm$^{-1}$; $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 2.87 (t, 2H, *J* 7.7 Hz, $OCH_2$–C*H*$_2$-Ph), 3.18 (dd, 1H, *J*

7.8 and 8.9 Hz, H-2), 3.22–3.32 (m, 2H, H-4 and H-5), 3.35 (t, 1H, *J* 7.8 and 8.9 Hz, H-3), 3.66 (dd, 1H, *J* 5.4 and 11.8 Hz, H-6a), 3.68–3.75 (m, 1H, OC*H*$_2$–CH$_2$-Ph), 3.86 (dd, 1H, *J* 2.0 and 11.9 Hz, H-6b), 4.01–4.08 (m, 1H, OC*H*$_2$–CH$_2$-Ph), 4.29 (d, 1H, *J* 7.6 Hz, H-1), 5.04 (s, 2H, OC*H*$_2$-Ph), 6.89 (dd, 2H, *J* 2.2 and 6.7 Hz, Ph), 7.16 (dd, 2H, *J* 2.0 and 6.6 Hz, Ph), 7.28–7.30 (m, 1H, Ph), 7.35 (t, 2H, *J* 6.6 Hz, Ph), 7.41 (dd, 2H, *J* 1.6 and 7.3 Hz, Ph). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 36.5, 62.9, 71.2, 71.8, 72.1, 75.3, 78.1, 78.3, 104.5 (C-1), 116.0 (2C), 128.6 (2C), 128.9, 129.6 (2C), 131.1 (2C), 132.6, 139.1, 158.9. ESIMS: *m*/*z* 408.1 ($M^+$+18); HRMS *m*/*z*: calcd for $C_{21}H_{26}O_7Na$, 413.1576; found, 413.1578. Anal. Calcd for $C_{21}H_{26}O_7$: C, 64.60; H, 6.71. Found: C, 64.43; H, 6.98.

### 1.4. 2-(4-Benzyloxyphenyl)ethyl 4,6-*O*-benzylidene-β-D-glucopyranoside (8)

To a solution of compound **7** (1.1 g, 2.82 mmol) and *p*-toluenesulfonic acid (50 mg) in DMF (10 mL) was added dropwise benzaldehyde dimethyl acetal (1 mL) with stirring. The reaction mixture was stirred at room temperature for 24 h and then diluted with EtOAc (100 mL). The organic layer was washed with water, and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic extracts were washed with water and brine, then dried (anhyd $Na_2SO_4$) and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography using 3:7 EtOAc–petroleum ether to afford **8** as a white solid: yield 1.28 g (95%); $R_f$ 0.7 (9:1 EtOAc–petroleum ether); mp 106–108 °C; $[\alpha]_D$ −31.6 (*c* 0.5, $CHCl_3$); IR (Neat): 3507, 2870, 1512, 1242, 1082, 1028 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.90 (t, 2H, *J* 7.9 Hz, OCH$_2$–C*H*$_2$-Ph), 3.43–3.50 (m, 2H, H-2 and H-5), 3.55 (t, 1H, *J* 9.3 Hz, H-3), 3.69–3.83 (m, 3H, H-4, H-6a and OC*H*$_2$–CH$_2$-Ph), 4.09–4.16 (m, 1H, OC*H*$_2$–CH$_2$-Ph), 4.33 (dd, 1H, *J* 4.8 and 10.5 Hz, H-6b), 4.38 (d, 1H, *J* 7.8 Hz, H-1), 5.04 (s, 2H, OC*H*$_2$-Ph), 5.53 (s, 1H, PhCH), 6.91 (dd, 2H, *J* 2.0 and 6.6 Hz, Ph), 7.14 (dd, 2H, *J* 1.9 and 6.7 Hz, Ph), 7.30–7.40 (m, 10H, Ph). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 35.1, 66.3, 68.6, 70.0, 71.2, 73.0, 74.5, 80.5, 101.8, 103.2 (C-1), 114.9 (2C), 126.2 (2C), 127.4 (2C), 127.9, 128.3 (2C), 128.5 (2C), 129.2, 129.8 (2C), 130.3, 136.9, 137.0, 157.4. ESIMS: *m*/*z* 496.3 ($M^+$+18), 479.2 ($M^+$+1); HRMS *m*/*z*: calcd for $C_{28}H_{30}O_7Na$, 501.1889; found, 501.1897. Anal. Calcd for $C_{28}H_{30}O_7$: C, 70.28; H, 6.32. Found: C, 70.20; H, 6.50.

### 1.5. 2-(4-Benzyloxyphenyl)ethyl 4,6-*O*-benzylidene-2,3-di-*O*-benzyl-β-D-glucopyranoside (9)

To an ice-cooled solution of compound **8** (0.35 g, 0.73 mmol) in DMF (5 mL), sodium hydride (76 mg, 1.9 mmol; 60% oil coated) was added portionwise with stirring for 15 min. Benzyl bromide (0.21 mL) was then added dropwise, and the mixture was stirred at room temperature for 20 h. The mixture was diluted with EtOAc (~50 mL) and washed with water. The aqueous layer was extracted with EtOAc (2 × 50 mL), and the combined organic extracts were washed with water and brine, then dried (anhyd $Na_2SO_4$) and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography using 15:85 EtOAc–petroleum ether to afford **9** as an off-white solid: yield 434 mg (90%); $R_f$ 0.58 (1:4 EtOAc–petroleum ether); mp 110–112 °C; $[\alpha]_D$ −22.6 (*c* 0.5, $CHCl_3$); IR: 2879, 1512, 1239, 1089, 1006 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.90 (t, 2H, *J* 7.0 Hz, OCH$_2$–C*H*$_2$-Ph), 3.36–3.41 (m, 1H, H-5), 3.44 (t, 1H, *J* 8.1 Hz, H-2), 3.67 (t, 2H, *J* 9.0 Hz, H-3), 3.70–3.80 (m, 3H, H-4, H-6a and OC*H*$_2$–CH$_2$-Ph), 4.11–4.16 (m, 1H, OC*H*$_2$–CH$_2$-Ph), 4.34 (dd, 1H, *J* 5.2 and 10.6 Hz, H-6b), 4.51 (d, 1H, *J* 7.6 Hz, H-1), 4.64 and 4.69 (2d, 2H, *J* 11.0 Hz, OCH$_2$Ph), 4.78 (d, 1H, *J* 11.2 Hz, OCH$_2$Ph), 4.89 (d, 1H, *J* 11.6 Hz, OCH$_2$Ph), 4.97 (s, 2H, OCH$_2$Ph), 5.55 (s, 1H, PhCH), 6.86 (dd, 2H, *J* 2.0 and 6.7 Hz, Ph), 7.14 (dd, 2H, *J* 2.1 and 6.7 Hz, Ph), 7.22–7.40 (m, 18H, Ph), 7.47–7.50 (m, 2H, Ph); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 30.9, 61.6, 64.3, 65.5, 66.7, 70.6, 70.7, 71.9, 72.6, 73.2, 96.7, 99.6 (C-1), 110.4 (2C), 121.5 (2C), 122.9 (2C), 123.1 (2C), 123.4 (2C), 123.5 (2C), 123.6 (2C), 123.76 (2C), 123.79 (2C), 124.1 (2C), 124.4 (2C), 125.4 (2C), 126.3, 132.7, 132.9, 133.9, 134.1, 153.0; ESIMS: *m*/*z* 676.5 ($M^+$+18); HRMS *m*/*z*: calcd for $C_{42}H_{42}O_7Na$, 681.2828; found, 681.2819. Anal. Calcd for $C_{42}H_{42}O_7$: C, 76.57; H, 6.43. Found: C, 76.89; H, 6.77.

### 1.6. 2-(4-Benzyloxyphenyl)ethyl 2,3-di-*O*-benzyl-β-D-glucopyranoside (10)

A solution of compound **9** (1.2 g, 1.82 mmol) in 80% aqueous HOAc (15 mL) was stirred at 80 °C for 90 min. The HOAc was evaporated under reduced pressure. The residue was dissolved in EtOAc (100 mL) and successively washed with water, satd aq $NaHCO_3$, water and brine, dried (anhyd $Na_2SO_4$) and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography using 1:1 EtOAc–petroleum ether to afford **10** as a white solid; yield 276 mg (82%); $R_f$ 0.62 (1:4 EtOAc–petroleum ether); mp 112–114 °C; $[\alpha]_D$ −15.4 (*c* 0.5, $CHCl_3$); IR: 3352, 2850, 1513, 1455, 1249, 1121, 1071, 1036 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.90 (t, 2H, *J* 7.0 Hz, OCH$_2$–C*H*$_2$-Ph), 3.28–3.32 (m, 1H, H-5), 3.40–3.42 (m, 2H, H-2 and H-6a), 3.53 (t, 1H, *J* 8.8 Hz, H-4), 3.70–3.78 (m, 2H, H-6b and OC*H*$_2$–CH$_2$-Ph), 3.85–3.97 (m, 1H, H-3), 4.11–4.17 (m, 1H, OC*H*$_2$–CH$_2$-Ph), 4.45 (d, 1H, *J* 7.2 Hz, H-1), 4.59 (d, 1H, *J* 10.8 Hz,

OC$H_2$-Ph), 4.64 (d, 1H, *J* 11.6 Hz, OC$H_2$-Ph), 4.74 (d, 1H, *J* 10.8 Hz, OC$H_2$-Ph), 4.94 (d, 1H, *J* 11.8 Hz, OC$H_2$-Ph), 4.97 (s, 2H, OC$H_2$-Ph), 6.87 (dd, 2H, *J* 1.9 and 6.7 Hz, Ph), 7.14 (d, 2H, *J* 8.8 Hz, Ph), 7.21–7.40 (m, 15H, Ph); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 35.3, 62.4, 69.9, 70.3, 71.0, 74.5, 74.9, 75.1, 81.8, 83.8, 103.7 (C-1), 114.8 (2C), 127.3 (2C), 127.6, 127.81 (2C), 127.83 (2C), 128.0 (2C), 128.2 (2C), 128.5 (4C), 129.8 (2C), 130.8, 137.0, 138.3, 138.5, 157.4; ESIMS: *m*/*z* 588.5 ($M^+$+18), 571.4 ($M^+$+1); HRMS *m*/*z*: calcd for $C_{35}H_{38}O_7Na$, 593.2515; found, 593.2521. Anal. Calcd for $C_{35}H_{38}O_7$: C, 73.66; H, 6.71. Found: C, 73.50; H, 6.88.

### 1.7. 2-(4-Benzyloxyphenyl)ethyl 2,3-di-*O*-benzyl-6-*O*-[(*E*)-4-*O*-benzylferuloyl]-β-D-glucopyranoside (14) and 2-(4-Benzyloxyphenyl)ethyl 2,3-di-*O*-benzyl-4-*O*-[(*E*)-4-*O*-benzylferuloyl]-β-D-glucopyranoside (15)

To a solution of 4-benzyloxy-3-methoxycinnamic acid (**13**, 148 mg, 0.526 mmol) and 4-dimethylaminopyridine (DMAP, 64 mg, 0.526 mmol) in $CH_2Cl_2$ (5 mL) was added compound **10** (0.3 g, 0.526 mmol) at room temperature with stirring for 10 min. 1-(3-Dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDCI, 101 mg, 0.526 mmol) was added with stirring at room temperature for a further 1 h. The reaction mixture was diluted with $CH_2Cl_2$ (100 mL), washed with water and brine, dried (anhyd $Na_2SO_4$) and then evaporated to dryness under reduced pressure. The crude product was purified by column chromatography using 1:9 EtOAc–petroleum ether to afford **14** and **15** as white solids.

**1.7.1. Data for 14.** Yield: 155 mg (35%); $R_f$ 0.66 (1:1 EtOAc–petroleum ether); mp 109–111 °C; $[\alpha]_D$ −9.6 (*c* 0.5, $CHCl_3$); IR: 3503, 2870, 1702, 1512, 1258, 1138, 1067 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.91 (t, 2H, *J* 7.2 Hz, OC$H_2$–C$H_2$-Ph), 3.43 (t, 1H, *J* 7.9 Hz, H-2), 3.45–3.55 (m, 3H, H-3, H-4, H-5), 3.72 (dd, 1H, *J* 5.7 and 9.1 Hz, OC$H_2$–C$H_2$-Ph), 3.91 (s, 3H, $OCH_3$), 4.13–4.19 (m, 1H, OC$H_2$–C$H_2$-Ph), 4.38 (dd, 1H, *J* 1.8 and 12.2 Hz, H-6a), 4.44 (d, 1H, *J* 7.5 Hz, H-1), 4.58 (dd, 1H, *J* 4.4 and 12.1 Hz, H-6b), 4.60 (d, 1H, *J* 11.6 Hz, OC$H_2$-Ph), 4.72 (d, 1H, *J* 8.6 Hz, OC$H_2$-Ph), 4.75 (d, 1H, *J* 8.3 Hz, OC$H_2$-Ph), 4.92 (d, 1H, *J* 11.6 Hz, OC$H_2$-Ph), 4.95 (s, 2H, OC$H_2$-Ph), 5.18 (s, 2H, OC$H_2$-Ph), 6.34 and 7.63 (2d, 2H, *J* 15.8 Hz, CH=CH–C=O), 6.81–6.88 (m, 3H, Ph), 7.01 (dd, 1H, *J* 1.9 and 8.3 Hz, Ph), 7.06 (d, 1H, *J* 1.9 Hz, Ph), 7.13 (d, 2H, *J* 8.8 Hz, Ph), 7.23–7.43 (m, 20H, Ph); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 35.3, 55.94, 55.97, 63.1, 69.9, 70.8, 71.0, 73.8, 74.6, 75.3, 81.7, 83.6, 103.9 (C-1), 110.2, 113.4, 114.8 (2C), 115.3, 119.0 (2C), 122.6, 127.2 (2C), 127.4 (2C), 127.58, 127.6, 127.8 (2C), 127.9 (2C), 128.0 (2C), 128.3 (2C), 128.5 (4C), 128.6, 129.8 (2C), 130.8, 136.5, 137.1, 138.4, 138.5, 145.5, 149.8, 150.4, 151.4, 167.6; ESIMS: *m*/*z* 854.5 ($M^+$+18), 831.5 ($M^+$+1); HRMS *m*/*z*: calcd for $C_{52}H_{52}O_{10}Na$, 859.3458; found, 859.3482. Anal. Calcd for $C_{52}H_{52}O_{10}$: C, 74.62; H, 6.26. Found: C, 74.29; H, 6.55.

**1.7.2. Data for 15.** Yield: 172 mg (39%); $R_f$ 0.66 (1:1 EtOAc–petroleum ether); mp 91–93 °C; $[\alpha]_D$ −56.8 (*c* 0.5, $CHCl_3$); IR: 3414, 2919, 1713, 1514, 1255, 1139, 1027 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.92 (t, 2H, *J* 7.0 Hz, OC$H_2$–C$H_2$-Ph), 3.36–3.41 (m, 1H, H-5), 3.51 (t, 1H, *J* 8.6 Hz, H-2), 3.57–3.63 (m, 1H, H-6a), 3.68–3.78 (m, 3H, H-3, H-6b and OC$H_2$–C$H_2$-Ph), 3.93 (s, 3H, $OCH_3$), 4.15–4.21 (m, 1H, OC$H_2$–C$H_2$-Ph), 4.48 (d, 1H, *J* 7.8 Hz, H-1), 4.62 (d, 1H, *J* 11.0 Hz, OC$H_2$-Ph), 4.66 (d, 1H, *J* 11.3 Hz, OC$H_2$-Ph), 4.74 (d, 1H, *J* 11.0 Hz, OC$H_2$-Ph), 4.80 (d, 1H, *J* 11.5 Hz, OC$H_2$-Ph), 4.98 (s, 2H, OC$H_2$-Ph), 5.05 (t, 1H, *J* 9.6 Hz, H-4), 5.20 (s, 2H, OC$H_2$-Ph), 6.14 and 7.59 (2d, 2H, *J* 15.8 Hz, CH=CH–C=O), 6.86–6.90 (m, 3H, Ph), 7.00–7.04 (m, 2H, Ph), 7.15 (d, 2H, *J* 8.6 Hz, Ph), 7.18–7.44 (m, 20H, Ph); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 35.3, 56.0, 61.5, 69.9, 70.4, 70.8, 70.9, 74.3, 74.8, 75.0, 81.3, 82.0, 103.6 (C-1), 110.4, 113.4, 114.6, 114.8 (2C), 122.7 (2C), 127.2 (2C), 127.4 (2C), 127.5, 127.6, 127.8, 127.98 (2C), 128.0, 128.1 (2C), 128.2 (2C), 128.3 (2C), 128.5 (2C), 128.6 (2C), 129.8 (2C), 130.8, 136.4, 137.1, 138.2, 138.3, 146.2, 149.8, 150.6, 157.4, 166.8; ESIMS: *m*/*z* 854.5 ($M^+$+18); HRMS *m*/*z*: calcd for $C_{52}H_{52}O_{10}Na$, 859.3458; found, 859.3453. Anal. Calcd for $C_{52}H_{52}O_{10}$: C, 74.62; H, 6.26. Found: C, 74.40; H, 6.60.

### 1.8. Preparation of 2-(4-hydroxyphenyl)ethyl 6-*O*-[(*E*)-feruloyl]-β-D-glucopyranoside (1)

A mixture of **14** (130 mg, 155 μmol), 5% Pd/C (155 mg) and 1,4-cyclohexadiene (291 μL, 3.11 mmol) in 1:1 DMF–EtOH (1.09 mL) was stirred at 40 °C for 10 h. The reaction mixture was filtered through Celite and the filtrate was concentrated to give a yellow residue. The residue was purified on preparative TLC using $CHCl_3$–MeOH to give 21.4 mg (29%) of grayanoside A. The physical constants of the product were in agreement with those reported in the literature.[12]

### 1.9. Preparation of 2-(4-hydroxyphenyl)ethyl 4-*O*-[(*E*)-feruloyl]-β-D-glucopyranoside (2)

A mixture of **15** (140 mg, 167 μmol), 5% Pd/C (167 mg), and 1,4-cyclohexadiene (314 μL, 3.36 mmol) in 1:1 DMF–EtOH (1.17 mL) was stirred at 40 °C for 10 h. The reaction mixture was filtered through Celite and the filtrate was concentrated to give a yellow residue. The residue was purified on preparative TLC using

$CHCl_3$–MeOH to give 22 mg (28%) of syringalide B. The physical constants were in agreement with those recorded earlier[13] for this compound.

## Acknowledgements

We are thankful to Professor J. Iqbal and Dr. R. Rajagopalan for their continuous encouragement to this work. We also thank the members of the Department of Analytical Research and Development, especially Mr. Vasudev R., for the analyses.

## References

1. Cometa, F.; Tomassini, L.; Nicoletti, M.; Pieretti, S. *Fitoterapia* **1993**, *64*, 195–217.
2. Kurkin, V. A. *Chem. Nat. Compd.* **2003**, *39*, 123–153.
3. Pan, J.; Yuan, C.; Lin, C.; Jia, Z.; Zheng, R. *Pharmazie* **2003**, *58*, 767–775.
4. Molgaard, P.; Ravn, H. *Phytochemistry* **1988**, *27*, 2411–2421.
5. Ravn, H.; Nishibe, S.; Sasahara, M.; Lu, X. B. *Phytochemistry* **1990**, *29*, 3627–3631.
6. Shoyama, Y.; Matsumoto, M.; Nishioka, I. *Phytochemistry* **1987**, *26*, 983–986.
7. Xiong, Q.; Hase, K.; Tezuka, Y.; Tani, T.; Namba, T.; Kadota, S. *Planta Med.* **1998**, *64*, 120–125.
8. Nakamura, T.; Okuyama, E.; Tsukada, A.; Yamaszaki, M.; Satake, M.; Nishibe, S.; Deyama, T.; Moriya, A.; Maruno, M.; Nishimura, H. *Chem. Pharm. Bull.* **1997**, *45*, 499–504.
9. Lin, L.-C.; Wang, Y.-H.; Hou, Y.-C.; Chang, S.; Liou, K.-T.; Chou, Y.-C.; Wang, W.-Y.; Shen, Y.-C. *J. Pharm. Pharmacol.* **2006**, *58*, 129–135.
10. Shimomura, H.; Sashida, Y.; Adachi, T. *Phytochemistry* **1987**, *26*, 2363–2366.
11. Kikuchi, M.; Yamauchi, Y.; Tanabe, F. *Yakugaku Zasshi* **1987**, *107*, 350–354; *Chem. Abstr.* **1987**, *107*, 130903.
12. Zhang, S.-Q.; Li, Z.-J.; Wang, A.-B.; Cai, M.-S.; Feng, R. *Carbohydr. Res.* **1997**, *299*, 281–285.
13. Li, Q.; Li, S.-C.; Li, H.; Cai, M.-S.; Li, Z.-J. *Carbohydr. Res.* **2005**, *340*, 1601–1604.
14. Kawada, T.; Asano, R.; Hayashida, S.; Sakuno, T. *J. Org. Chem.* **1999**, *64*, 9268–9271.
15. Das, S. K.; Reddy, K. A.; Krovvidi, V. L. N. R.; Mukkanti, K. *Carbohydr. Res.* **2005**, *340*, 1387–1392.
16. Kerékgyártó, J.; Kamerling, J. P.; Bouwstra, J. B.; Vliegenthart, J. F. G.; Lipták, A. *Carbohydr. Res.* **1989**, *186*, 51–62.
17. Kerékgyártó, J.; Szurmai, Z.; Lipták, A. *Carbohydr. Res.* **1993**, *245*, 65–80.
18. Wegmann, B.; Schmidt, R. R. *J. Carbohydr. Chem.* **1987**, *6*, 357–375.
19. Magnusson, G.; Ahlfors, S.; Dahmén, J.; Jansson, K.; Nilsson, U.; Noori, G.; Stenvall, K.; Tjornebo, A. *J. Org. Chem.* **1990**, *55*, 3932–3946.
20. Leschot, A.; Tapia, R. A.; Eyzaguirre, J. *Synth. Commun.* **2002**, *32*, 3219–3224.
21. Kim, I.-H.; Heirtzler, F. R.; Morisseau, C.; Nishi, K.; Tsai, H.-J.; Hammock, B. D. *J. Med. Chem.* **2005**, *48*, 3621–3629.
22. Lohray, B. B.; Jayamma, Y.; Chatterjee, M. *J. Org. Chem.* **1995**, *60*, 5958–5960.
23. Panek, J. S.; Beresis, R. T.; Celatka, C. A. *J. Org. Chem.* **1996**, *61*, 6494–6495.
24. Rodebaugh, R.; Debenham, J. S.; Fraser-Reid, B. *Tetrahedron Lett.* **1996**, *37*, 5477–5478.