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Carbohydrate Research 299 (1997) 281–285

CARBOHYDRATE RESEARCH

Total synthesis of the phenylpropanoid glycoside, grayanoside A [1]

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Received 9 April 1996; accepted in revised form 12 January 1997

Abstract

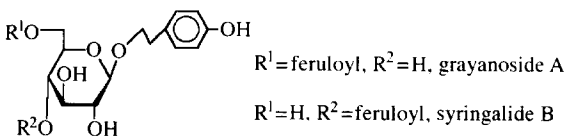
Grayanoside A, 2-(4-hydroxyphenyl)ethyl 6-*O*-feruloyl-β-D-glucopyranoside, was synthesized for the first time by using chloroacetyl groups for the protection of hydroxy functions. 2-(4-Allyloxyphenyl)ethyl 4-*O*-[(4-*O*-allyl)feruloyl]-2,3,6-tri-*O*-chloroacetyl-β-D-glucopyranoside (**12**) was synthesized from 2-(4-allyloxyphenyl)ethyl 4,6-*O*-benzylidene-β-D-glucopyranoside (**8**) in four steps with the goal of preparing syringalide B. It was found, however, that the feruloyl group migrated from the 4- to the 6-position of the glycopyranoside during the deprotection of **12**. © 1997 Elsevier Science Ltd.

Keywords: Grayanoside A; Chloroacetyl groups; Syringalide B; Glycopyranoside

1. Introduction

Phenylpropanoid glycosides are natural glycosides having a substituted cinnamoyl residue attached to a hydroxy group and a substituted phenylethyl group as aglycon. Most of them possess potent biological activities such as antiviral, antitumor, and antifungal, and are immunomodulatory agents [1–5]. Until now, about a hundred phenylpropanoid glycosides have been isolated and identified by their spectra and by chemical conversions.

In a previous paper, we reported that the sugar core from phenylpropanoid glycosides could be synthesized using the Koenigs–Knorr or trichloroacetate method [6]. However, a total synthesis has not yet been reported. Grayanoside A, a monosaccharide phenylpropanoid glycoside, was isolated from the bark of *Pranus grayana* [7], and Syringalide B, an isomer of grayanoside A, was isolated from *Syringa reticulata* leaf [8]. This paper reports the first synthesis of grayanoside A and uses chloroacetyl groups for the protection of hydroxy functions.



2. Results and discussion

Phenylpropanoid glycosides have hydroxy groups in the sugar ring, in the aglycon, and in the feruloyl

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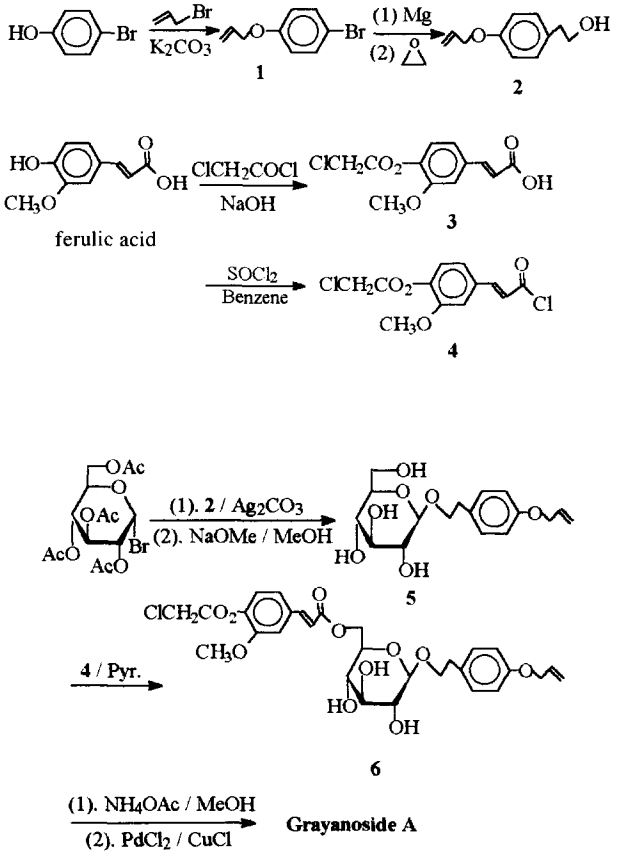
[1] Part 20 of the series Studies on Glycosides.

PII S0008-6215(97)00032-3

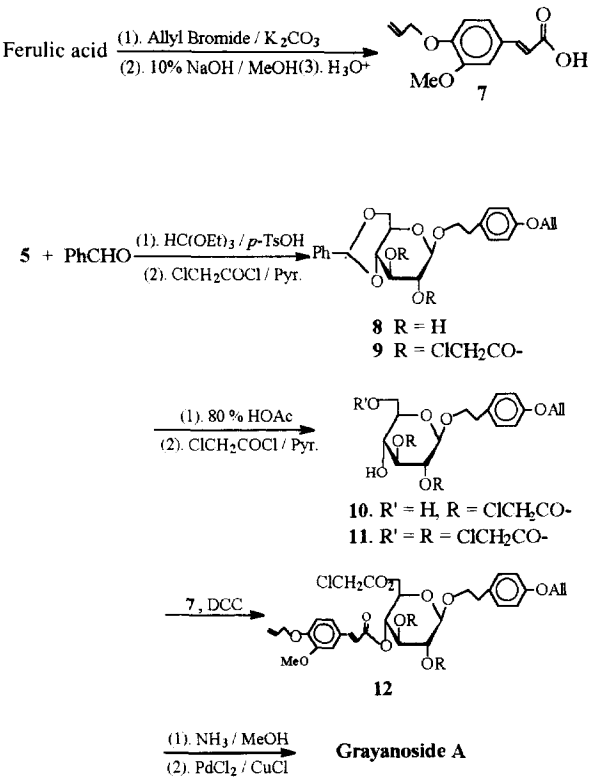
residue, as well as a double bond and an ester linkage. Consequently, it is difficult to choose appropriate protective groups for their synthesis. After consideration of all the functions present, the allyl group was chosen for protecting the phenol in the aglycon because the allyl ether is easy to prepare, is stable under both acidic and basic conditions, and can be removed by specific reagents. We chose chloroacetyl groups to protect the other hydroxy functions. The designed synthetic route for grayanoside A is as follows.



Refluxing a mixture of *p*-bromophenol, allyl bromide, and acetone in the presence of potassium carbonate gave *p*-allyloxyphenyl bromide (**1**), which was converted into 2-(4-allyloxyphenyl)ethanol (**2**) via a Grignard reaction. The hydroxy group in ferulic acid was protected as the chloroacetate, and the corresponding acid (**3**) and acid chloride (**4**) were then prepared.

2-(4-Allyloxyphenyl)ethyl β-D-glucopyranoside (**5**) was obtained by glycosylation of **3** under the Koenigs–Knorr conditions, followed by deacetylation. Regioselective feruloylation of **5** with an equimolar amount of acid chloride **4** afforded the partially protected grayanoside A (**6**). The chloroacetyl group in **6** was removed by refluxing **6** with NH_4OAc in methanol. The allyl ether in the aglycon was cleaved by means of $PdCl_2$–CuCl [9] to afford the total synthesis of grayanoside A.

In order to synthesize the isomer of grayanoside A having the feruloyl group at the 4-position of the β-D-glucopyranoside, namely Syringalide B, the following route was designed.



A mixture of ferulic acid, allyl bromide, potassium carbonate, and acetone was heated under reflux. Hydrolysis of the resulting crude ester with 10% NaOH (aq) and then acidification gave 4-*O*-allylferulic acid (**7**). Compound **5**, freshly distilled benzaldehyde, and triethyl orthofomate were heated under reflux in the presence of a catalytic amount of *p*-TsOH · H_2O in THF. Purification of the crude product by chromatography afforded **8**, which could not be crystallized from various solvents. However, chloroacetylation of **8** afforded **9**, which could be crystallized from methanol, ethanol, or petroleum ether–ethyl acetate. Acetic acid (80%) was used to remove the benzylidene group in **9**. Refluxing **9** with methanol–water, ethanol–water, and 2-propanol–water, respectively, in the presence of *p*-toluenesulfonic acid could also remove the benzylidene group, but the reaction was slow, and the procedure was often accompanied by partial cleavage of the chloroacetyl protecting groups.

Reaction of **10** with an equimolar amount of chloroacetyl chloride at low temperature (−15 °C) gave compound **11** regioselectively. When compound **7**, DCC, and DMAP were used to acylate the 4-OH group of compound **11** in refluxing dichloromethane, compound **12** was obtained in good yield. The three chloroacetyl groups in **12** were removed selectively by using 15% NH_3–MeOH at 5–10 °C, and the allyl ether was cleaved by using $PdCl_2$–CuCl. The crude, deprotected product was purified by flash column chromatography. Unexpectedly, the ^{13}C NMR data of the product were the same as those of grayanoside A. The data indicated that the feruloyl was attached to O-6 of the glucosyl unit. The feruloyl group had evidently migrated from the 4- to the 6-position upon removal of the three chloroacetyl groups.

3. Experimental

General methods.—Melting points are uncorrected. Spectra were recorded with the following instruments: ^1H and ^{13}C NMR, JEOL FX-90Q (90 MHz) and JEOL GX-400 (400 MHz); ^1H–^1H COSY, HETCOR, NOESY, JEOL GX-400; mass spectra, VG 20-250 GLC–MS and VG ZAB GC GLC–MS. The ^1H NMR spectra were recorded with Me_4Si as the internal standard and the ^{13}C NMR spectra with $CDCl_3$ as solvent and internal standard. Optical rotations were measured at 22–25 °C with a Perkin–Elmer 243 polarimeter in $CHCl_3$ solns. The progress of reactions was monitored by TLC on GF254 (Hai Yang Chemical Factory, Qing Dao, Shandong, PR China). Column chromatography was performed on silica gel H (10–40 μm) (Hai Yang Chemical Factory, Qingdao, Shandong, PR China). The solvent systems indicated are volume–volume ratios. Components were detected by spraying the plates with 20% concd H_2SO_4 in EtOH and heating. Elemental analyses were performed on Perkin–Elmer 240C instrument.

4-Allyloxyphenyl bromide (**1**).—Potassium carbonate (75 g, 0.54 mmol) was added to a stirred soln of 4-bromophenol (98 g, 0.57 mmol), allyl bromide (71 g, 0.59 mmol), and acetone (200 mL). The mixture was refluxed with stirring for 4 h and then filtered. Concentration of the filtrate in vacuo afforded a colorless liquid (107 g, 88.8%), bp 100–103 °C/6 mm Hg.

2-(4-Allyloxyphenyl)ethanol (**2**).—Grignard reagent was prepared by using magnesium (12.5 g, 0.52 mol) and compound **1** (107g, 0.50 mol) under standard conditions (200 mL ether, 80 mL THF and cooling to 5 °C). A soln of ethylene oxide (22.9 g, 0.52 mol, diluted with 70 mL of anhyd THF) was added dropwise below 10° C to the Grignard reagent. The mixture was stirred for another 2 h at room temperature. A soln of satd NH_4Cl (200 mL) was added dropwise to this mixture. The organic phase was separated, washed with brine (100 mL), and dried with Na_2SO_4. Removal of the solvent in vacuo gave **2** (56.0 g, 62.9%), bp 128–130 °C; IR: ν 3342, 1643, 1606, 1506 cm^{-1}; ^1H NMR (90 MHz): δ_H 7.14–7.04 (d, 2 H, Ar–H), 6.86–6.76 (d, 2 H, Ar–H), 6.24–5.82 (m, 1 H, CH=), 5.66–5.16 (m, 2 H, $=CH_2$), 4.48–4.40 (m, 2 H, O–CH_2–C=C), 3.78–3.62 (t, 2 H, O–CH_2), 2.80–2.64 (t, 2 H, Ar–CH_2); ^{13}C NMR: δ_C 156.8, 130.6, 129.4, 114.5 (Ar), 133.2, 116.8, 68.4 (O–C–C=C), 63.0 (O–C), 37.8 (Ar–C).

(E)-4-O-Chloroacetylferulic acid (**3**).—Chloroacetyl chloride (7.0 g, 62 mmol) was added at 0 °C to a stirred soln of (*E*)-ferulic acid (40 g, 20 mmol) in aq NaOH (3 *M*, 30 mL) and the resulting suspension was stirred for 3 min. Concentrated HCl soln (4 mL) was added, and the mixture was filtered. Recrystallization of the crude product from EtOH–water gave **3** (4.20 g, 75.3%), mp 146–148 °C; IR: ν 1780, 1673 cm^{-1}; MS (EI) (*m/z*) 270, 194, 177, 149.

(E)-4-O-Chloroacetylferuloyl chloride (**4**).—A mixture of **3** (3.5 g, 1.28 mmol), $SOCl_2$ (4.5 mL, 3.8 equiv), and anhyd benzene (50 mL) was refluxed for 50 min and evaporated to dryness. Toluene (30 mL) was added and the mixture was evaporated to dryness again. Crystallization from anhyd toluene (30 mL) gave **4** (3.6 g, 93.0%), mp 81–83 °C; MS (EI) (*m/z*) 289.

2-(4-Allyloxyphenyl)ethyl β-D-glucopyranoside (**5**).—A mixture of tetra-*O*-acetyl-α-D-glucopyranosyl bromide (40.0 g, 97 mmol), **2** (17.0 g, 97 mmol), Ag_2Co_3 (27 g, 98 mmol), and anhyd C_6H_6–CH_3NO_2 (1:1, 80 mL) was stirred at room temperature for 10 h in the dark. The mixture was filtered and the filtrate evaporated under diminished pressure to dryness. A soln of NaOH in MeOH (prepared by adding 1.0 g of sodium to 100 mL of MeOH) was added and the mixture was stirred for 1 h. Concentrated HCl (2.0 mL) was added and the soln was evaporated, and the residue was purified by column chromatography (15:1 $CHCl_3$–MeOH) to give **5** as a waxy solid, 21.0 g, yield 65.0%. IR: ν 3406, 1643, 1607 cm^{-1}; ^1H NMR (90 MHz): δ_H 7.43–6.80 (dd, 4 H, Ar–H), 6.30–5.90 (m, 1 H, CH=C), 5.53–5.22 (m, 2 H, C=CH_2), 4.56–4.50 (dd, 2 H, O–CH_2–C=C), 4.42–4.33 (d, 1 H, H-1), 4.16–3.50 (m, 8 H, O–CH), 2.96–2.82 (t, 2

H, Ar–CH_2). MS (FAB): 341 $[M + 1]^+$. Anal. Calcd for $C_{17}H_{24}O_7$: C, 59.99; H, 7.11. Found: C, 60.05; H, 7.04.

2-(4-Allyloxyphenyl)ethyl 6-O-[(E)-O-chloroacetylferuloyl]-β-D-glucopyranoside (**6**).—Compound **4** (1.5 g, 5.5 mmol) was added at 0 °C to a soln of **5** (1.5 g, 4.4 mmol), CH_2Cl_2 (20 mL), and pyridine (2 mL). The mixture was stirred at 10 °C for 20 h. The solvent was evaporated and the residue was dissolved in EtOAc (50 mL). The organic layer was washed successively with water, HCl (1 M), and brine (3 × 30 mL), dried (Na_2SO_4), and evaporated. Flash column chromatography (silica gel H, 5:1:0.1 benzene–$CHCl_3$–MeOH) gave **6** as a waxy solid; 1.5 g (61.5%); $[\alpha]_D$ −53.8° (*c*, 0.66, $CHCl_3$); IR: ν 3416, 1777, 1700, 1633 cm^{-1}; ^1H NMR (400 MHz): δ_H 7.05–6.98 (m, 5 H, Ar–H), 6.73 (d, 2 H, Ar–H), 7.58, 6.38 (d, *J* 15.8 Hz, CH=CH–C=O), 5.35, 5.23 (dd, 2H, C=CH_2), 5.98 (m, 1 H, CH=C), 4.50 (s, 2 H, –O–CH_2–C=C), 4.32 (s, 2 H, –CH_2–C=O), 4.34 (d, 1 H, *J* 8.79 Hz, H-1), 3.72–3.44 (m, 5 H, H-2, H-3, H-4, H-5, O–CH), 3.77 (s, 3 H, CH_3O–), 2.85 (m, 2 H, CH_2–Ar); ^{13}C NMR: δ_C 157.1, 151.0, 140.8, 133.5, 130.1, 129.8 122.8, 121.2, 114.6, 111.4 (Ar), 144.7, 117.9, 165.1 (C=C–C=O), 68.6, 133.3, 117.4 (O–C–C=C), 102.8 (C-1), 73.9 (C-2), 76.1 (C-3), 70.2 (C-4), 73.5 (C-5), 63.7 (C-6), 40.5, 167.1 (Cl–C–C=O), 55.9 (CH_3O–), 71.2, 35.2 (O–C–C). MS (FAB): 632 $[M + K]^+$, 253, 177, 161. Anal. Calcd for $C_{29}H_{33}O_{11}Cl$: C, 58.77; H, 5.62; Cl, 5.91. Found: C, 58.82; H, 5.61; Cl, 5.92.

2-(4-Hydroxyphenyl)ethyl 6-O-[(E)-feruloyl]-β-D-glucopyranoside (grayanoside A).—A soln of **6** (600 mg, 1.01 mmol), NH_4OAc (0.5 g, 6.5 mmol), and MeOH (15 mL) was refluxed for 1 h, and the solvent was evaporated. The residue was purified on a short column (3 cm, silica gel H) and the product was dissolved in 10 mL MeOH along with $PdCl_2$ (0.18 g, 1.0 mmol) and CuCl (0.1 g, 1.0 mmol). The mixture was stirred vigorously at 25 °C for 4 h, filtered through Celite (1 cm), and the filtrate was evaporated. Flash column chromatography (10:5:2 $CHCl_3$–benzene–MeOH) gave grayanoside A (380 mg, 79.0); ^1H NMR (400 MHz, CD_3OD): δ_H 7.14 (s, 1 H, Ar–H), 7.02 (d, 2 H, Ar–H), 6.99 (d, 1 H, Ar–H), 6.80 (d, 1 H, Ar–H), 6.64 (d, 2 H, Ar–H), 7.62, 6.37 (d, 2 H, *J* 15.8 Hz, CH=CH–C=O), 3.88 (s, 3 H, CH_3O–), 4.32 (d, 1 H, *J* 7.1 Hz, H), 3.58–3.38 (m, 2 H, H-2, H-3), 3.21 (dd, 1 H, H-4), 3.52 (m, 1 H, H-5), 4.50, 4.35 (dd, 2 H, H-6a, H-6b), 3.94 (m, 1 H), 3.72 (m, 1 H) (O–CH_2), 2.83 (m, 2 H, CH_2–Ar); ^{13}C NMR: δ_C 157.6, 151.4, 150.2, 131.7, 131.4, 128.4, 125.5, 117.3, 116.9, 112.3 (Ar), 169.9, 147.9, 116.0 (C=C–C=O), 105.4 (C-1), 76.2 (C-2), 78.7 (C-3), 72.6 (C-4), 75.8 (C-5), 65.5 (C-6), 73.3, 37.3 (O–CH_2CH_2), 57.2 (CH_3O–) MS (FAB): 516 $[M + K + 1]^+$, 177, 136, 121. Anal. Calcd for $C_{24}H_{28}O_{10}$: C, 60.48; H, 5.93. Found: C, 60.56; H, 5.90.

4-O-Allylferulic acid (**7**).—To a mixture of ferulic acid (15.0 g, 77 mmol), allyl bromide (17 mL, 200 mmol), and acetone (200 mL), potassium carbonate (27.5 g, 200 mmol) was added under vigorous stirring. The mixture was refluxed with stirring for 6 h, cooled, and filtered. The solvent was evaporated. To the residue was added 10% NaOH (25 mL) and MeOH (25 mL). The soln was refluxed for 30 min, cooled, and acidified with HCl (6 M), filtered, and recrystallized from 1:1 petroleum ether–EtOAc to give **7** (10.1 g, 55.8%), mp 150.0–152.0 °C; IR: ν 1674, 1619 cm^{-1}. MS (FAB) (*m/z*) 234, 271.

2-(4-Allyloxyphenyl)ethyl 4,6-O-benzylidene-β-D-glucopyranoside (**8**).—A mixture of **5** (21.0 g, 61.8 mmol), PhCHO (8 mL), triethyl orthoformate (10 mL), *p*-toluenesulfonic acid monohydrate (0.5 g, 2.6 mmol), and anhyd THF (100 mL) was refluxed for 5 h, cooled to about 4 °C, K_2CO_3 (0.5 g) was added, and the mixture was evaporated. Column chromatography (1:1 petroleum ether–EtOAc) gave **8** (21.5 g, waxy solid, 81.3%); $[\alpha]_D$ −25° (*c* 0.48, $CHCl_3$); IR: ν 3502, 3198, 1640 cm^{-1}; ^{13}C NMR (100 MHz): δ_C 157.3, 136.9, 130.2, 129.8, 129.0, 128.3,126.3,114.8 (Ar), 133.3,117.6, 68.8, (O–C–C=C), 101.9 (O–CH–O), 103.3 (C-1), 74.5 (C-3), 73.0 (C-2), 80.5 (C-4), 66.4 (C-5), 68.6 (C-6), 71.3, 35.2 (O–CH_2CH_2–); MS (FAB): 428 $[M^+]$, 251, 161. Anal. Calcd for: $C_{24}H_{28}O_7$: C, 67.26; H, 6.59. Found: C, 67.15; H, 6.60.

2-(4-Allyloxyphenyl)ethyl 2,3-di-O-chloroacetyl-4,6-O-benzylidene-β-D-glucopyranoside (**9**).—To a soln of **8** (3.1 g, 7.2 mmol), CH_2Cl_2 (20 mL), and pyridine (2 mL) cooled to 0 °C was added, dropwise during 20 min, chloroacetyl chloride (1.5 mL, diluted with 5 mL of CH_2Cl_2). The mixture was stirred for 2 h at room temperature and washed at 0 °C successively with water, HCl (1 M), $NaHCO_3$ (3%), and brine (4 × 15 mL), dried (Na_2SO_4), and concd. The residue was recrystallized from 1:2 petroleum ether–EtOAc (15 mL) to give compound **9** (3.6 g, 85.5%); $[\alpha]_D$ −33° (*c* 0.40, $CHCl_3$); mp 87–89 °C; IR: ν 1745 cm^{-1}; ^1H NMR (500 MHz): δ_H 7.44–7.35 (m, 5 H, Ar–H), 7.09 (d, 2 H, Ar–H), 6.85 (d, 2 H, Ar–H), 5.49 (s, 1 H, O–CH–O), 6.05 (m, 1 H, O–CH=C), 5.42, 5.28 (dd, 2 H, C=CH_2), 4.54 (dd,

2 H, O–CH_2–C=C), 4.58 (d, 1 H, *J* 7.8 Hz, H-1), 5.06 (dd, 1 H, H-2), 5.35 (dd, 1 H, H-3), 3.74 (dd, 1 H, H-4), 3.53 (m, 1 H, H-5), 4.38, 3.80 (2 × dd, 2 × 1 H, H-6a, H-6b), 4.12 (m, 1 H), 3.66 (m, 1 H) (O–CH_2), 2.83 (m, 2 H, CH_2–Ar), 4.05 (s, 2 H), 3.88 (d, 2 H) (ClCH_2–C=O); ^{13}C NMR (125 MHz): δ_C 157.2, 130.5, 136.5, 129.8, 129.2, 126.1, 128.3, 114.8, 114.6 (Ar), 133.3, 117.6, 68.8 (O–C–C=C), 101.7 (O–CH–O), 100.9 (C-1), 73.2 (C-2), 73.4 (C-3), 78.0 (C-4), 66.3 (C-5), 68.5 (C-6), 71.1, 35.0 (O–CH_2CH_2), 166.7, 166.1, 40.5, 40.4 (Cl–CH_2C=O). Anal. Calcd for $C_{28}H_{10}O_4C_{12}$: C, 70.00; H, 2.10; Cl, 14.57. Found: C, 69.96; H, 2.13; Cl, 14.36.

*2-(4-Allyloxyphenyl)ethyl 2,3-di-*O*-chloroacetyl-β-*D*-glucopyranoside* (**10**).—A mixture of **9** (3.5 g, 6.0 mmol) and 80% AcOH (50 mL) was stirred at 80 °C for 2 h and then toluene (50 mL) was added, and the solvent was evaporated off under diminished pressure. Chloroform (30 mL) was added and the organic layer was washed at 0 °C with water, $NaHCO_3$ (5%), and brine (3 × 20 mL), dried (Na_2SO_4), and concd. Flash column chromatography (silica gel H, 1:1 petroleum ether–EtOAc) gave **10** (2.2 g, syrup, 75.1%); IR: ν 3452, 1745 cm^{-1}. MS (FAB): 492 $[M]^+$.

*2-(4-Allyloxyphenyl)ethyl 2,3,6-tri-*O*-chloroacetyl-β-*D*-glucopyranoside* (**11**).—To a soln of **10** (2.2 g, 4.46 mmol), anhyd CH_2Cl_2 (20 mL), and anhyd pyridine (2 mL) cooled to −15 °C was added, dropwise during 30 min, chloroacetyl chloride (0.36 mL, diluted by 5 mL of CH_2Cl_2), and the mixture was stirred for 4 h. The subsequent treatment was the same as that of **10**, and gave **11** (1.8 g, syrup, 76%); IR: ν 3448, 1747, 1728 cm^{-1}. MS (FAB): 569 $[M + 1]^+$.

*2-(4-Allyloxyphenyl)ethyl 4-*O*-[(*E*)-(*O*-allyl)feruloyl]-2,3,6-tri-*O*-chloroacetyl-β-*D*-glucopyranoside* (**12**).—A mixture of **11** (1.2 g, 2.1 mmol), **7** (0.65 g, 2.78 mmol), DCC (0.32 g, 1.55 mmol), DMAP (10 mg), and anhyd CH_2Cl_2 (10 mL) was refluxed for 2 h. The soln was evaporated and the residue was purified by flash column chromatography (19:1 benzene–EtOAc) to give **12** (1.25 g, 75.5%); IR: ν 1765, 1752, 1704, 1622 cm^{-1}; ^{1}H NMR (400 MHz): δ_H 7.09–7.03 (m, 4 H, Ar–H), 6.87–6.84 (m, 3 H, Ar–H), 7.52 (d, 1 H), 6.19 (d, 1 H, *J* 15.9 Hz) (CH=CH–C=O), 5.44 (m, 2 H), 5.29 (m, 2 H), 6.04 (m, 2 H) (2 × CH=CH_2), 4.52 (m, 4 H, O–CH_2–C=C), 4.55 (d, 1 H, *J* 7.9 Hz, H-1), 5.08 (t, 1 H, H-2), 5.26 (1 H, H-3), 5.38 (1 H, H-4), 3.64 (1 H, H-5), 4.66, 4.33 (m, 2 H, H-6a, H-6b), 3.91 (s, 3 H, OCH_3), 4.12, 4.10, 3.96, (6 H, 3 × ClCH_2), 4.14 (m), 3.77 (m) (O–CH_2), 2.83 (m, 2 H, CH_2–Ar); ^{13}C NMR (100 MHz): δ_C 157.2, 130.5, 129.8 (Ar), 157.0, 149.5, 126.8, 123.1, 112.7, 110.0 (Ar), 147.3, 113.3, 165.5 (C=C–C=O), 68.8, 133.3, 117.7 (O–C–C=C), 69.7, 132.6, 118.5 (O–C–C=O), 100.4 (C-1), 71.7 (C-2), 74.0 (C-3), 67.9 (C-4), 72.5 (C-5), 63.5 (C-6), 71.1, 34.9 (O–C–C), 40.3, 40.4, 40.7, 165.9, 166.0, 167.0 (3 × Cl–CH_2–C=O), 55.9 (CH_3O); MS (FAB): 787 [M + 1], 608, 217, 177. Anal. Calcd for $C_{36}H_{39}Cl_3O_{13}$: C, 55.00; H, 5.00; Cl, 13.53. Found: C, 54.72; H, 5.06; Cl, 13.68.

*2-(4-Hydroxyphenyl)ethyl 6-*O*-[(*E*)-feruloyl]-β-*D*-glucopyranoside*.—A mixture of **12** (0.7 g, 8.9 mol), NH_3–CH_3OH (15%, 10 mL), and $CHCl_3$ (10 mL) was stirred at 5–10 °C for 1.5 h, and then $CHCl_3$ (30 mL) and brine (20 mL) were added. The organic layer was separated, washed with brine (30 mL), dried (Na_2SO_4), and concd. The residue was purified by flash column chromatography to give a product (0.36 g), which was mixed with $PdCl_2$ (230 mg, 1.3 mol), CuCl (120 mg, 1.21 mmol), MeOH (10 mL), and water (2 mL). The mixture was stirred strongly at 25 °C for 4 h. The purification was the same as for grayanoside A and afforded a product (200 mg, 47.8%, two steps). All the spectral data were the same as those for grayanoside A.

Acknowledgements

This investigation was supported by a grant No. 29302008 from the National Natural Science Foundation of PR China.

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