Total Synthesis of Resvebassianol A, a Metabolite of Resveratrol by Beauveria bassiana

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Abstract: Resveratrol is a well-known dietary polyphenol because it has a variety of beneficial biological activities. The fungus Beauveria bassiana is one of the most frequently used microorganisms for the biotransformation of polyphenols. Recently, resvebassianol A (2), a glycosylated metabolite of resveratrol by B. bassiana, was isolated and structurally elucidated. It was demonstrated to exhibit antioxidant, regenerative, and anti-inflammatory activities with no cytotoxicity. Here, we report the first total synthesis of resvebassianol A, 4′-O-β-(4′′′-O-methylglucopyranosyl)resveratrol (2), and its regiomer, 3-O-β-(4′′′-O-methylglucopyranosyl)resveratrol (3). Key reactions include (i) the construction of a stilbene core via a novel Heck reaction of aryl halides and styrenes, and (ii) glycosylation with unnatural methylglucopyranosyl bromide. The glycosylation step was carefully optimized by varying the bases and solvents. Resveratrol metabolites 2 and 3 were obtained at 7.5% and 6.3% of the overall yield, respectively.

Keywords: resveratrol; resvebassianol A; Beauveria bassiana; metabolites; glycosylation

1. Introduction

Resveratrol (1, trans-3,5,4-trihydroxystilbene) is an important dietary polyphenol and naturally occurring phytoalexin found in grapes, red wine, berries, peanuts, olive oil, etc. [1–3]. It is produced by plants in response to environmental stress and fungal attack through the induction of resveratrol synthetase [4,5]. Resveratrol was first isolated from the roots of the white hellebore lily (Veratrum grandiflorum O. Loes) in 1940 [6]. Most of the biological activities of resveratrol have been shown by its trans stilbene isomer, while the cis stilbene isomer also occurs naturally [7]. Resveratrol exerts numerous biological activities such as antioxidant, anti-infective, anti-inflammatory, anti-ischemic, cardioprotective, neuroprotective, anti-aging, anti-viral, anti-obesity, and anti-cancer effects [8–18]. Recently, it was revealed that its ability to activate various deacetylase enzymes (sirtuins) could be responsible for the various biological properties and delay aging [19,20]. Despite their pharmacological activities, various in vivo studies have shown that the potential of polyphenols is impaired by their insolubility in water, ultraviolet light instability, poor intestinal absorption, short half-life, rapid clearance, low bioavailability, and rapid metabolism [21,22]. The introduction of a glycosyl moiety on polyphenols not only helps to enhance the solubility of substrates but also reduces their toxicity, which ultimately increases the activity of biosynthetic intermediates [23]. Moreover, the sugar moiety of polyphenol glycosides might play a major role in their absorption, resulting in an acceptable concentration in the circulatory streams [24]. Polyphenols are subjected to enzymatic oxidation by polyphenol oxidases in plants, during food processing, and also after human consumption, which can be protected by glycosylation [25]. The incorporation of sugar moieties into different types of pharmacophores, natural products, or prodrugs has been proven to improve anti-cancer activities [26]. Several glycosyl derivatives of resveratrol have been recognized in the roots of Polygonum cuspidatum such as piceid (3-O-β-D-glucosyl resveratrol), resveratroloside (4′-O-
Several glycosyl derivatives of resveratrol have been recognized in resveratrol and its regioisomer, 3-O-β-(4‴-O-methylglucopyranosyl)resveratrol (3).

Figure 1. Chemical structures of resveratrol 1, resvebassianol A (2), and 3-O-β-(4‴-O-methylglucopyranosyl) resveratrol 3.
2. Materials and Methods

2.1. Chemical Reagents

All chemicals and solvents were reagent grade and were purchased from Sigma Aldrich (Saint Louis, MO, USA), TCI (Tokyo, Japan), and Alfa Aesar (Haverhill, MA, USA). All reagents were used directly without further purification.

2.2. Purification and Instrumentation

All reactions were carried out in an inert atmosphere in flame-dried glassware. Reactions were monitored by thin-layer chromatography using 0.25 mm silica gel plates and visualized using UV 254/286 nm. Flash chromatography was carried out using silica gel 60 (230–400 mesh, Merck, Darmstadt, Germany) as the stationary phase. Data for $^1H$ and $^{13}C$ NMR spectra are reported as chemical shifts (multiplicity, coupling constants, integration), and multiplicities are reported as s = singlet, d = doublet, t = triplet, q = quartet, septet = septet, m = multiplet and/or multiple resonances, number of protons, and coupling constant (J).

High-resolution mass spectra (HRMS) were recorded using electrospray ionization (ESI) mass spectroscopy on a JEOL JMS- 700 (FAB and EI) and an Agilent 6530 Q-TOF LC/MS/MS system (ESI).

2.3. General Experimental Procedure

2.3.1. Synthesis of Methyl 4, 6-O-Benzylidene-α-D-Glucopyranoside (13)

Methyl α-D-glucopyranoside 8 (10 g, 51.5 mmol) was dissolved in anhydrous N,N-dimethylformamide (100 mL) under a N$_2$ atmosphere, p-toluene sulfonic acid (1.62 g, 9.4 mmol) was added, followed by the addition of benzaldehyde dimethyl acetal (9.2 mL, 61.8 mmol), and the solution was stirred under N$_2$ for 16 h. After completion of the reaction, triethylamine (4 mL) was added to the reaction, which was then diluted with ethyl acetate. The organic layer was subsequently washed with saturated sodium bicarbonate and brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (methanol/dichloromethane = 30:1) to yield product 13 (12 g, 93%) as a white solid.

$^1H$ NMR (600 MHz, CDCl$_3$) $\delta$ 7.49–7.47 (m, Ph, 2H), 7.36–7.34 (m, Ph, 3H), 5.49 (s, 1H), 4.70 (d, $J$ = 3.9 Hz, 1H), 4.25 (dd, $J$ = 6, 6 Hz, 1H), 3.87 (t, $J$ = 9 Hz, 1H), 3.76–3.74 (m, 1H), 3.69 (t, $J$ = 12 Hz, 1H), 3.57–3.53 (m, 2H), 3.43 (t, $J$ = 12 Hz, 1H), 3.39 (s, 3H), 2.93 (d, $J$ = 6 Hz, 1H); $^{13}C$ NMR (151 MHz, CDCl$_3$) $\delta$ 137.0, 129.2, 128.3, 126.4, 101.9, 99.9, 80.9, 72.7, 71.4, 68.9, 62.3, 55.5; HRMS (ESI): mass calcd for C$_{14}$H$_{18}$O$_6$ [M + H]$^+$, 283.1176; found, 283.1168.

2.3.2. Synthesis of Methyl 2,3-di-O-Benzyl-4,6-O-Benzylidene-α-D-Glucopyranoside (14)

Methyl 4,6-O-benzylidene-α-D-glucopyranoside 13 (11.5 g, 40.73 mmol) was dissolved in anhydrous N,N-dimethylformamide (100 mL) under a N$_2$ atmosphere. The solution was cooled to 0 °C in an ice bath, after which NaH (60% dispersion in mineral oil, 4 g, 163 mmol) was added, and the reaction was stirred for 1 h at room temperature. The solution was cooled to 0 °C, and benzyl bromide (14.5 mL, 122 mmol) was added dropwise. The solution was stirred at room temperature overnight, after which methanol (10 mL) was added, and the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1:7) to yield product 14 (17.5 g, 92%) as a white solid compound.

$^1H$ NMR (600 MHz, CDCl$_3$) $\delta$ 7.49 (d, $J$ = 6, 2H), 7.39–7.21 (m, 13H), 5.54 (s, 1H), 4.70 (d, $J$ = 6 Hz, 1H), 4.84 (dd, $J$ = 12 Hz, 1H), 4.70 (d, $J$ = 12 Hz, 1H), 4.60 (d, $J$ = 6 Hz, 1H), 4.26 (dd, $J$ = 12, 6 Hz, 1H), 4.05 (t, $J$ = 9 Hz, 1H), 3.84–3.80 (m, 1H), 3.70 (t, $J$ = 9 Hz, 1H), 3.60 (t, $J$ = 9 Hz, 1H), 3.55 (dd, $J$ = 3 Hz, 1H), 3.39 (s, 3H); $^{13}C$ NMR (151 MHz, CDCl$_3$) $\delta$ 138.8, 138.2, 137.5, 129.0, 128.5, 128.4, 128.3, 128.2, 128.1, 128, 127.7, 126.1, 101.3, 99.3, 82.2, 79.2, 78.6, 75.4, 73.8, 69.1, 62.4, 55.4; HRMS (ESI): mass calcd for C$_{28}$H$_{30}$O$_6$ [M + H]$^+$, 463.2115; found, 463.2112.
2.3.3. Synthesis of Methyl 2,3,6-tri-O-Benzyl-α-D-Glucopyranoside (15)

Methyl 2,3-di-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside 14 (17.25 g, 38 mmol) was dissolved in anhydrous CH₂Cl₂ (100 mL) under a N₂ atmosphere, and the solution was cooled to 0 °C. Et₃SiH (30 mL, 186 mmol) and trifluoroacetic acid (14 mL, 186 mmol) were added, and the solution was stirred at 0 °C for 4 h. The reaction was quenched with Et₃N and methanol. CH₂Cl₂ was added, and the solution was washed with water and brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The mixture was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1:2) to afford product 15 (12 g, 91%) as a colorless oil. ¹H NMR (600 MHz, CDCl₃) δ 7.37–7.26 (m, 15H), 5 (d, J = 12 Hz, 1H), 4.76 (dd, J = 12 Hz, 2H), 4.76–4.63 (m, 2H), 4.59 (d, J = 12 Hz, 1H), 4.54 (d, J = 12, 1H), 3.79 (t, J = 12, 18 Hz, 1H), 3.71–3.68 (m, 3H), 3.61 (t, J = 12, 18 Hz, 1H), 3.54 (dd, J = 6 Hz, 1H), 3.38 (s, 3H), 2.33 (s, 1H); ¹³C NMR (151 MHz, CDCl₃) δ 138.8, 138.1, 138.0, 128.6, 128.5, 128.4, 128.1, 128.0, 127.9, 127.7, 127.6, 98.2, 81.5, 79.6, 77.2, 77.0, 76.7, 75.4, 73.6, 73.2, 70.7, 69.9, 69.5, 55.3; HRMS (ESI): mass calcd for C₃₀H₃₂O₆ [M + NH₄]⁺, 487.2537; found, 487.2525.

2.3.4. Synthesis of Methyl 2,3,6-Tri-O-Benzyl-α-D-Glucopyranoside (16)

NaH (60% dispersion in mineral oil, 1.5 g, 63 mmol) was added to a solution of methyl 2,3,6-tri-O-benzyl-α-D-glucopyranoside 15 (11.5 g, 25 mmol) in anhydrous N,N-dimethylformamide (100 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, and methyl iodide (3.8 mL, 63 mmol) was added to the reaction mixture. The reaction mixture was stirred overnight at room temperature. The reaction was quenched with methanol and ice-cold water and then extracted with ethyl acetate. The collected organic layers were washed with brine, dried with Na₂SO₄, and concentrated under reduced pressure. The mixture was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1:2) to afford product 16 (11.2 g, 95%) as a viscous liquid. ¹H NMR (600 MHz, CDCl₃) δ 7.39–7.26 (m, 5H), 4.93 (d, J = 10.8, 1H), 4.83–4.74 (m, 2H), 4.67–4.57 (m, 3H), 4.51 (d, J = 12.1 Hz, 1H), 3.86 (s, 1H), 3.66 (dd, J = 22.7, 7.1 Hz, 3H), 3.50 (dd, J = 9.7, 3.5 Hz, 1H), 3.46 (s, 3H), 3.37 (s, 3H), 3.35 (s, 1H); ¹³C NMR (151 MHz, CDCl₃) δ 138.9, 138.2, 138.0, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.6, 98.2, 82.1, 79.6, 79.4, 75.7, 73.5, 73.4, 70.1, 68.6, 60.7, 55.2; HRMS (ESI): mass calcd for C₂₉H₃₄O₆ [M + NH₄]⁺, 496.2694; found, 496.2688.

2.3.5. Synthesis of Methyl 4-O-Methyl-α-D-Glucopyranoside (17)

Pd (10%/C) (3 g) was added to a solution of methyl 2,3,6-Tri-O-methyl-4,6-O-benzylidene-α-D-glucopyranoside 16 (11 g, 22 mmol) in anhydrous methanol (100 mL), and the mixture was stirred under an atmosphere of hydrogen at room temperature for 24 h. The catalyst was filtered out, and the solvents were removed under reduced pressure. The crude residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1:1) to afford the viscous product 17 (4.6 g, 95%). ¹H NMR (600 MHz, CD₂OD) δ 4.69 (s, 1H), 3.78 (d, J = 11.7 Hz, 1H), 3.70 (dq, J = 12.2, 6.9, 4.4 Hz, 2H), 3.57 (s, 3H), 3.53–3.47 (m, 1H), 3.44 (d, J = 7.9 Hz, 1H), 3.40 (s, 3H), 3.10 (t, J = 9.3 Hz, 1H); ¹³C NMR (151 MHz, CD₂OD) δ 99.7, 79.6, 73.7, 72.1, 71.2, 60.8, 59.5, 54.2; HRMS (ESI): mass calcd for C₈H₁₆O₆ [M + H]⁺, 209.1020; found, 209.1033.

2.3.6. Synthesis of Methyl 2,3,6-tri-O-Acetyl-α-D-Glucopyranoside (18)

Compound 17 (4.5 g, 22 mmol) was dissolved in acetic anhydride (25 mL, 217 mmol) and pyridine (25 mL, 217 mmol) and stirred at room temperature for 12 h. After completion of the reaction, pyridine and acetic anhydride were removed in vacuo. The residue was dissolved in CH₂Cl₂ and washed with dilute HCl. The organic layer was collected, washed with brine, dried with MgSO₄, and concentrated under reduced pressure. The mixture was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1:4) to afford the viscous product 18 (5.1 g, 71%). ¹H NMR (600 MHz, CDCl₃) δ 5.50–5.42 (m, 1H), 4.88–4.79 (m, 2H), 4.35 (d, J = 10.0 Hz, 1H), 4.30–4.24 (m, 1H), 3.88–3.81 (m, 1H), 3.42 (d, J = 3.7 Hz, 3H), 3.39 (d, J = 3.9 Hz, 3H), 3.34 (dd, J = 12.6, 6.3 Hz, 1H), 2.12 (d, J = 3.9 Hz, 3H), 2.08...
(d, J = 6.0 Hz, 6H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\) 170.7, 170.4, 169.8, 96.8, 77.8, 71.9, 71.1, 68.2, 62.7, 60.1, 55.3, 20.9, 20.8, 20.8; HRMS (ESI): mass calcd for C\(_{14}\)H\(_{22}\)O\(_9\) [M + NH\(_4\)]\(^+\), 352.1602; found, 352.1605.

2.3.7. Synthesis of 1,2,3,6-Tetra-O-Acetyl-4-O-Methyl-\(\alpha\)-D-Glucopyranoside (19)

To a stirred solution of 18 (5 g, 15 mmol) in acetic anhydride (50 mL) at 0 \(^\circ\)C, boron trifluoride ether trifluoride ether (2 mL, 15 mmol) was added. The solution was warmed to room temperature and allowed to stir for 2 h. Then, the solution was poured into an ice-cold saturated solution of NaHCO\(_3\) and extracted with ethyl acetate. The combined organic layers were separated, dried over MgSO\(_4\), and concentrated under reduced pressure. The mixture was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1:2) to yield the viscous product 19 (4.1 g, 75%). \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 6.53 (d, \(J\) = 6.6 Hz, 6H), 2.10 (s, 3H); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\) 170.5, 170.4, 169.8, 96.8, 77.8, 71.9, 71.1, 68.2, 62.7, 60.1, 55.3, 20.9, 20.8, 20.8; HRMS (ESI): mass calcd for C\(_{15}\)H\(_{22}\)O\(_9\) [M + NH\(_4\)]\(^+\), 380.1551; found, 380.1545.

2.3.8. Synthesis of 2,3,6-O-Triacetyl-4-O-Methylglucopyranosyl bromide (6)

A solution of HBr (10 mL, 33 wt% in acetic acid) was added dropwise to a stirred solution of compound 18 (3.7 g, 10 mmol) in CH\(_2\)Cl\(_2\) (50 mL) at 0 \(^\circ\)C. The solution was stirred at room temperature for 4 h. After completion of the reaction, the reaction mixture was quenched carefully with ice water and diluted with CH\(_2\)Cl\(_2\) and water. The organic layer was separated and washed with saturated NaHCO\(_3\) and brine. The organic layer was dried over MgSO\(_4\), filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethylacetate/n-hexane 1:4) to yield the light yellow liquid 6 (2.8 g, 73%). This compound was unstable, and after drying, it was used for further reactions. \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 6.51 (d, \(J\) = 10.0, 3.8 Hz, 1H), 4.39 (d, \(J\) = 12.4 Hz, 1H), 4.31 (dd, \(J\) = 12.4, 4.0 Hz, 1H), 4.15 (d, \(J\) = 10.1 Hz, 1H), 3.45 (d, \(J\) = 9.7 Hz, 4H), 2.12 (d, \(J\) = 6.6 Hz, 6H), 2.10 (s, 3H); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\) 170.5, 170.1, 169.6, 86.8, 76.6, 73.2, 71.8, 70.9, 61.8, 60.3, 20.9, 20.8, 20.8, 20.7.

2.3.9. Synthesis of 3,5-bis(tert-Butyldimethylsilyloxy) Benzaldehyde (20)

To a well-stirred solution of methyltriphenylphosphonium bromide (2.2 g, 20 mmol) in anhydrous THF was refluxed for 1 h for in situ generation of methylenetriphenylphosphorane. Upon returning to room temperature, a solution of compound 18 (5 g, 15 mmol) in anhydrous THF was added, and the reaction was heated to reflux overnight. After completion of the reaction, ethyl acetate was added, and the solution was washed with water, dried over anhydrous Na\(_2\)SO\(_4\), filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1:25) to yield
product **21** (3.4 g, 68%) as a colorless oil. **1H NMR** (600 MHz, CDCl$_3$) $\delta$ 6.6 (dd, $J = 17.4$, 10.9 Hz, 1H), 6.5 (s, 2H), 6.3 (s, 1H), 5.7 (d, $J = 17.5$ Hz, 1H), 5.2 (d, $J = 10.9$ Hz, 1H), 1.0 (s, 18H), 0.2 (s, 12H); **13C NMR** (151 MHz, CDCl$_3$) $\delta$ 156.6, 139.4, 136.7, 113.9, 111.7, 111.5, 25.7, 25.7, 18.2; HRMS (ESI): mass calcd for C$_{30}$H$_{36}$O$_2$Si$_2$[M + H]$^+$, 365.2327; found, 365.2333.

2.3.11. Synthesis of 5-Vinylbenzene-1,3-diol, [3,5-Dihydroxy Styrene] (12)

To a solution of (5-vinyl-1,3-phenylene) bis(oxy)bis(tert-butyldimethylsilane) **21** (3 g, 8.2 mmol) in anhydrous THF (15 mL), TBAF (4 mL, 14 mmol) was added at 0°C. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1:4) to yield **5-vinyl-1,3-phenylene diacetate** (565 mg, 57%) as a white solid.

2.3.12. Synthesis of 5-Vinyl-1,3-Phenylene Diacetate (3,5-Diacetoxystyrene) (5)

Acetic anhydride (2 mL, 22 mmol) was added dropwise to a solution of compound **12** (1 g, 7.3 mmol), pyridine (1.9 mL, 22 mmol), and DMAP (26 mg, 0.219 mmol) in CH$_2$Cl$_2$ at 0°C. The reaction mixture was stirred at room temperature for 12 h. The solution was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1:4) to yield **5-vinyl-1,3-phenylene diacetate** 5 (1.12 g, 70%) as a clear oil.

2.3.13. Synthesis of 4-Iodophenyln Acetate (11)

To a well-stirred mixture of 4-iodophenol **7** (2 g, 9 mmol) in dry pyridine (6 mL), acetic anhydride (1.75 mL, 18 mmol) was added at room temperature under N$_2$. The mixture was then stirred for 12 h. After completion of the reaction, water was added and extracted with CH$_2$Cl$_2$. The organic layer was dried over MgSO$_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane 100%) to yield **product 11** (2.2 g, 95%) as a white solid. **1H NMR** (600 MHz, CDCl$_3$) $\delta$ 7.7–7.6 (m, 2H), 6.9–6.8 (m, 2H), 2.3 (s, 3H); **13C NMR** (151 MHz, CDCl$_3$) $\delta$ 169.1, 151.2, 139.9, 135.3, 116.7, 115.9, 114.7, 21.0; HRMS (ESI): mass calcd for C$_{12}$H$_{12}$O$_4$[M + NH$_4$]$^+$, 238.1074; found, 238.1085.

2.3.14. Synthesis of 4-Iodophenol-2′,3′,6′-O-triacetyl-4′-O-Methylglucopyranoside (4)

To a mixture of iodophenol **7** (259 mg, 1.9 mmol) and 2,3,6-O-triacetyl-4-methylglucopyranosyl bromide 6 (730 mg, 1.9 mmol) in CHCl$_3$, benzyltributylammonium chloride (60 mg, 0.19 mmol) and potassium carbonate (665 mg, 4.8 mmol) were added and stirred at room temperature for 24 h. The reaction mixture was neutralized with 1 N HCl, and the organic layer was separated. The organic layer was washed with water-saturated NaHCO$_3$ and brine, dried over MgSO$_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1:4) to yield product **4** (565 mg, 57%) as a white solid. **1H NMR** (600 MHz, CDCl$_3$) $\delta$ 7.56–7.54 (m, 2H), 6.74 (dd, $J = 8.9$, 2.7 Hz 2H), 5.22 (t, $J = 9.3$ Hz, 1H), 5.12 (dd, $J = 9.6$, 7.7 Hz, 1H), 4.98 (d, $J = 7.8$ Hz, 1H), 4.38 (dd, $J = 12.0$, 2.4 Hz, 1H), 4.24 (dd, $J = 12.1$, 5.6 Hz, 1H), 3.67 (dd, $J = 10.1$, 5.7, 2.4 Hz, 1H), 3.43 (d, $J = 2.5$ Hz, 4H), 2.08 (d, $J = 8.5$ Hz, 6H), 2.03 (d, $J = 2.5$ Hz, 3H); **13C NMR** (151 MHz, CDCl$_3$) $\delta$ 170.5, 170.0, 169.6, 156.7, 138.4, 119.2, 98.7, 86.0, 77.5, 74.7, 73.1, 71.5, 62.7, 60.5, 20.9, 20.8, 20.7; HRMS (ESI): mass calcd for C$_{19}$H$_{23}$O$_9$[M + NH$_4$]$^+$, 540.0725; found, 540.0712.
2.3.15. Synthesis of (E)-1"-(3,5-Diacetoxy)-2"-(4'-O-2",3",6"'-Triacetyl-4"'-O-Methyl-β-D-Glucopyranosidophenyl) Ethene (22)

To a solution of 3,5-diacetoxystyrene 5 (235 mg, 1.07 mmol) and compound 4 (560 mg, 1.07 mmol) in acetonitrile, palladium(II) acetate (0.012 mg, 0.053 mmol), benzyltriethylammonium chloride (243 mg,1.07 mmol), and tributylamine (0.68 mL, 2.9 mmol) were added and stirred at 100 °C for 2 h, N₂. After 2 h, the mixture was cooled to room temperature, filtered through a short Celite pad, and then evaporated to dryness. The residue was taken up in dichloromethane, washed with diluted HCl, water, and brine, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1:2) to yield compound 22 (361 mg, 55%) as a white crystal. 

2.3.16. Synthesis of 4'-O-β- (4'-O-Methylglucopyranosyl)Resveratrol (2)

Compound 22 (350 mg, 0.58 mmol) was dissolved in methanol (20 mL) and 0.2 M methanolic solution of sodium methoxide (20 mL). The resulting mixture was stirred for 1 h at room temperature. After completion of the reaction, the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methanol/dichloromethane = 1:8) to yield the final compound 2 (195 mg, 85%) as a white powder. 

2.3.17. Synthesis of 3-Hydroxy-5-Vinylphenyl-2',3',6'-tri-O-Acetyl-4'-O-Methyl-β-D-Glucopyranoside (10)

To a solution of dihydroxystyrene 12 (248 mg, 1.8 mmol) and 2,3,6-O-triacetyl-4-methylglucopyranosyl bromide 6 (700 mg, 1.8 mmol) in CHCl₃, benzyltributylammonium chloride (56 mg, 0.18 mmol) and potassium carbonate (636 mg, 4.6 mmol) were added and stirred at room temperature for 24 h. The reaction mixture was neutralized with 1 N HCl, and the organic layer was separated. The organic layer was washed with saturated NaHCO₃ and brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1:2) to yield product 10 (320 mg, 40%) as a white product. 

2.3.18. Synthesis of 3-Acetoxy-5-Vinylphenyl-2',3',6'-tri-O-Acetyl-4'-O-Methyl-β-D-Glucopyranoside (23)

Compound 10 (310 mg, 0.7 mmol) in CH₂Cl₂ (5 mL) at room temperature was added to pyridine (0.1 mL, 1.06 mmol) and 4-dimethylaminopyridine (0.001 mg), and acetic
anhydride (0.1 mL, 1.06 mmol) was added dropwise. The resulting mixture was stirred for 1 h. The mixture was diluted with CH₂Cl₂ and water. The organic phase was separated and washed with dilute hydrochloric acid, water, and brine, dried over anhydrous MgSO₄, filtered, and dried under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1:4) to yield product 23 (288 mg, 85%) as a white solid. ¹H NMR (600 MHz, CDCl₃) δ 8.66 (dd, J = 30.6, 2.0 Hz, 2H), 6.65–6.56 (m, 2H), 5.74–5.68 (m, 1H), 5.31–5.20 (m, 2H), 5.14 (ddt, J = 10.5, 7.8, 1.1 Hz, 1H), 5.05 (d, J = 7.7 Hz, 1H), 4.40 (dq, J = 12.0, 1.6 Hz, 1H), 4.27–4.20 (m, 1H), 3.75–3.68 (m, 1H), 3.47–3.39 (m, 5H), 2.27 (dd, J = 2.4, 1.1 Hz, 3H), 2.09 (dd, J = 2.3, 1.1 Hz, 3H), 2.07 (dd, J = 2.3, 1.1 Hz, 3H), 2.04 (dd, J = 2.3, 1.1 Hz, 3H); ¹³C NMR (151 MHz, CDCl₃) δ 170.6, 170.0, 169.7, 169.1, 157.5, 151.5, 140.0, 135.6, 115.6, 114.2, 112.1, 109.8, 98.6, 77.7, 74.7, 73.1, 71.5, 62.9, 60.4, 21.1, 20.9, 20.7, 20.7; HRMS (ESI): mass calcd for C₃₂H₂₈O₁₁[M + NH₄]⁺, 498.1970; found, 498.1985.

2.3.19. Synthesis of (E)-1”-(3-Acetoxy-5-O-2‴,3‴,6‴-Triacetyl-4‴-O-Methyl-β-D Glucopyranosidophenyl)- 2‴-(4‴-Acetoxyphenyl) Ethene (24)

To a solution of 4-iodophenylacetate 11 (147 mg, 0.56 mmol), compound 23 (270 mg, 0.56 mmol) in acetonitrile was added with palladium(II) acetate (0.006 mg, 0.028 mmol), triphenylphosphine oxide (0.1 mL, 1.06 mmol) and stirred at 100 °C for 2 h under nitrogen. After 2 h, the mixture was cooled to room temperature, filtered through a short Celite pad, and then evaporated to dryness. The residue was taken up in dichloromethane, washed with diluted hydrochloric acid, water, and brine, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1:2) to yield product 24 (275 mg, 80%) as a white crystal. ¹H NMR (600 MHz, CDCl₃) δ 7.5 (d, J = 8.0 Hz, 2H), 7.1–7.0 (m, 3H), 7.0–6.9 (m, 3H), 6.6 (s, 1H), 5.3 (t, J = 9.2 Hz, 1H), 5.2 (t, J = 8.5 Hz, 1H), 5.1 (d, J = 7.6 Hz, 1H), 4.4 (d, J = 11.9 Hz, 1H), 4.3 (dd, J = 11.4, 5.8 Hz, 1H), 3.7 (s, 1H), 3.5 (s, 4H), 2.3 (s, 6H), 2.1 (s, 3H), 2.1 (s, 6H); ¹³C NMR (151 MHz, CDCl₃) δ 171.0, 170.6, 170.0, 169.7, 169.1, 157.5, 151.3, 139.7, 131.9, 129.8, 127.9, 126.0, 117.1, 116.8, 114.2, 98.7, 77.6, 74.8, 73.1, 71.6, 62.7, 60.5, 21.1, 20.9, 20.8, 20.7; HRMS (ESI): mass calcd for C₃₁H₂₇O₁₅[M + H]⁺, 637.1999; found, 637.2014.

2.3.20. Synthesis of 3-O-β-(4‴′′-O-Methylglucopyranosyl) Resveratrol (3)

Compound 24 (260 mg, 0.64 mmol) was dissolved in methanol (20 mL), and 0.2 M methanolic solution of sodium methoxide (20 mL) was added at room temperature. The resulting mixture was stirred for 1 h. The mixture was concentrated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (methanol/dichloromethane = 1:8) to yield product 3 (217 mg, 84%) as a white powder. ¹H NMR (600 MHz, (CD₂)₂CO) δ 7.36 (d, J = 7.9 Hz, 2H), 7.03 (d, J = 16.3 Hz, 1H), 6.85 (d, J = 16.3 Hz, 1H), 6.79 (d, J = 8.1 Hz, 2H), 6.72 (s, 1H), 6.64 (s, 1H), 6.41 (s, 1H), 4.86 (d, J = 7.7 Hz, 1H), 3.81 (d, J = 12.0 Hz, 1H), 3.65 (dd, J = 12.0, 4.6 Hz, 1H), 3.59 (t, J = 9.0 Hz, 1H), 3.52 (s, 3H), 3.46–3.37 (m, 2H), 3.16 (t, J = 9.3 Hz, 1H); ¹³C NMR (151 MHz, (CD₂)₂CO) δ 159.3, 158.8, 157.7, 139.9, 128.7, 127.9, 125.4, 115.6, 107.3, 105.3, 102.9, 100.8, 79.2, 77.1, 76.1, 74.1, 61.2, 59.6; HRMS (ESI): mass calcd for C₂₁H₂₃O₈[M + NH₄]⁺, 405.1544; found, 405.1551.

The spectra of the above mentioned compounds is displayed in the part of Supplemental Material.

3. Results and Discussion

3.1. Retrosynthesis

Metabolite 2 and its regiomer 3 consist of a glycone attached to the aglycone moiety. The gycone moiety is 4-O-methyl glucopyranose, whereas the aglycone is a functional resveratrol featuring a stilbene core with a polyhydroxy group. Metabolite 2 is a structure in which 4-O-methylglucopyranose is attached to the 7-position hydroxyl group of resveratrol, whereas its regiomer 3 consists of a glycosyl moiety attached to the 3-position hydroxyl group of resveratrol. The synthesis of both metabolites involves a glycosylation reaction
that introduces methylated glucose as the core reaction and the Heck reaction to form a stilbene skeleton [34].

Schemes 1 and 2 provide a retrosynthetic methodology for the synthesis of both metabolites 2 and 3. Stilbene moiety 2 and its regiomer 3 were constructed via palladium-catalyzed Heck coupling. The rate-limiting step of the glycosylation reaction was performed with selectively protected compound 6 and commercially available iodophenol 7. Compound 10 was obtained from the glycosylation of compound 6 and styrene 12, which was synthesized from readily available dihydroxy benzaldehyde 9.

Scheme 1. Retrosynthetic analysis of 3-O-β-(4‴-O-methylglucopyranosyl)resveratrol 2.

Scheme 2. Retrosynthetic analysis of 3-O-β-(4‴-O-methylglucopyranosyl)resveratrol 3.

3.2. Chemistry

The reaction commenced with the preparation of the glycosyl donor, 4-O-methylglycopyranosyl bromide 6, as shown in Scheme 3, which involves eight steps from commercially available methyl-α-D-glucopyranoside 8. Regioselective protection of 4, 6-diol from the
starting material was accomplished by the introduction of a 4,6-O-benzylidene group using benzaldehyde dimethyl acetal under acidic conditions, yielding protected compound 13. 2,3-Di-O-benzylation of 13 generated 14 using NaH and BnBr. Further regioselective opening of the benzylidene ring of intermediate 14 was conducted with the help of triethylsilane (TES) and trifluoroacetic acid (TFA) to obtain alcohol 15 [35]. Methylation of compound 15 with NaH and MeI in N,N-dimethylformamide yielded product 16, followed by hydrogenolysis to yield product 17. Acetylation of the hydroxy groups of 17 was performed using pyridine and acetic anhydride to yield 18, followed by the replacement of an anomeric methoxy group with an acetoxy group using boron trifluoride diethyl etherate to yield 19. Finally, grafting of the anomeric acetoxy group was performed to incorporate bromine using HBr (33% in acetic acid) to yield acylated glycosyl bromide 6 at 73% [36]. As the final compound, 4-O-methylglucopyranosyl bromide 6, has poor chemical stability, it is suitable to obtain a large amount of acetate compound 19 and synthesize 6 immediately when necessary.

![Scheme 3. Synthesis of 4-O-methylglucopyranosyl bromide 6.](image)

3.5. Dihydroxystyrene 12 and 3,5 diacetoxy styrene 5 were synthesized from commercially available 3,5-dihydroxy benzaldehyde 9 according to Scheme 4. Protection of the hydroxy group of 9 with TBDMS yielded 20, and the Wittig reaction yielded olefin 21 using methyltriphenylphosphonium bromide under basic conditions. The TBDMS group in intermediate 21 was removed using tetrabutylammonium fluoride (TBAF) to furnish dihydroxy styrene 12, and further acetylation of both hydroxy groups resulted in 12 at 70% yield.
Scheme 4. Synthesis of diacetoxystyrene 5 and dihydroxystyrene 12.

After obtaining 6 and 12, the next target was to synthesize substrates 4 and 10, which participate in the Heck reaction for the synthesis of the stilbene core.

We performed glycosylation of both iodophenol 7 and dihydroxystyrene 12 separately with 4-O-methylglycopyranosyl bromide 6 under different reaction conditions, as shown in Tables 1 and 2. Using Ag$_2$CO$_3$ in acetonitrile produced low-yield glycoside products 4 and 10 up to 16% and 19%, respectively. We attempted to improve glycosylation using a phase transfer catalyst (TBAB) in a two-phase system (aqueous NaOH and K$_2$CO$_3$) in CHCl$_3$. Unfortunately, the reaction yielded trace amounts. The reaction was incomplete, and the substrate was recovered for reuse. Bromide compound 6 can be decomposed into glycal by an alkaline water phase and phenoxide anion [37]. Therefore, excess use of water in the reaction lowers the yield of the compound. After utilizing several conditions (Tables 1 and 2), the glycosylation reaction under the phase transfer catalyst BnNBu$_3$Cl and K$_2$CO$_3$ as a base at room temperature yielded product 4 at 57% yield. The desired mono-glycosylated product 10 was obtained at 40% yield along with the undesired di-glycosylated product as a mixture, which was separated by column chromatography.

Table 1. Optimization of glycosylation reaction for synthesis of 4.$^a$

| Entry | Base | Reagent | Solvent | Temp. (°C) | Yield (%)$^d$ |
|-------|------|---------|---------|------------|--------------|
| 1     |      | Ag$_2$CO$_3$ (1eq) | CH$_3$CN | r.t        | 16           |
| 2$^b$ | NaOH | TBAB    | CHCl$_3$:H$_2$O (1:1) | 45         | 14           |
| 3$^b$ | K$_2$CO$_3$ | TBAB | CHCl$_3$:H$_2$O (1:1) | 45         | 17           |
| 4$^c$ | K$_2$CO$_3$ | BnNBu$_3$Cl | CHCl$_3$ | r.t        | 57           |

$^a$ Reaction was carried out using 1 equiv of both starting materials 7 and 6. $^b$ Base (1.1 eq), TBAB (0.2 eq). $^c$ Base (2.5 eq), and BnNBu$_3$Cl (0.1 eq). $^d$ Isolated yield.
Table 2. Optimization of glycosylation reaction for synthesis of 10.

| Entry | Base          | Reagent         | Solvent       | Temp. (°C) | Yield (%) |
|-------|---------------|-----------------|---------------|------------|-----------|
| 1     | NaOH          | Ag₂CO₃          | CH₂CN         | r.t        | 19        |
| 2     | NaOH          | TBAB            | CHCl₂:CH₃O (1:1) | 45         | 13        |
| 3     | K₂CO₃        | TBAB            | CHCl₂:CH₃O (1:1) | 45         | 15        |
| 4     | K₂CO₃        | BnNBu₃Cl       | CHCl₃         | r.t        | 40        |

* Reaction was carried out using 1 equiv of both starting materials 6 and 12, ** Base (1.1 eq), TBAB (0.2 eq), *** Base (2.5 eq), and BnNBu₃Cl (0.1 eq). d Isolated yield.

Aryl iodide 7 was the choice for palladium-catalyzed Heck coupling because of its greater reactivity over other aryl halides.

The palladium-catalyzed Heck reaction between glycosylated compounds 4 and 5 under (Pd(OAc)₂, BnEt₂N⁺Cl⁻, Bu₃N) in warm acetonitrile produced 22 at 55% yield. Deprotection of the acetyl protecting groups of 22 under a methanolic solution of sodium methoxide resulted in metabolite 2 at 85% yield.

The hydroxy group of glycosylated product 10 was protected by acetylation to yield 23. Similar to Scheme 5, the protected product 23 undergoes a palladium-catalyzed Heck reaction with 4-iodophenyl acetate 11 to build styrene compound 24 at 80% yield. Finally, basic hydrolysis of the acetyl protecting groups under a methanolic solution of sodium methoxide afforded another metabolite, 3, at 84% yield (Scheme 6).

Scheme 5. Synthesis of 4′-O-β-(4‴-O-methylglucopyranosyl)resveratrol (2).

Scheme 6. Synthesis of 3-O-β-(4‴-O-methylglucopyranosyl)resveratrol (3).
4. Conclusions

In conclusion, an efficient total synthesis was performed for the preparation of resvebassianol A (2, a metabolite of resveratrol by Beauveria bassiana) and its regioemer 3 through glycosylation and a palladium-catalyzed Heck reaction. Resvebassianol A and regioemer 3 were synthesized in 11 and 12 linear steps, with overall yields of 7.5% and 6.3%, respectively. Incorporation of 4-O methyl glyosyl was performed through the glycosylation reaction and was optimized using a phase transfer catalyst with varying bases. This resulted in an elevated yield of up to 40% and 57%, respectively. Thus, this method can be helpful for the synthesis of metabolites that are difficult to obtain from plant sources and through microbial biotransformation. This strategy can also be used for the synthesis of other related metabolites.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/antioxidants110101509/s1, Figure S1: 1H-NMR (600 MHz, CDCl$_3$) of compound 13, Figure S2: 13C-NMR (150 MHz, CDCl$_3$) of compound 13, Figure S3: 1H-NMR (600 MHz, CDCl$_3$) of compound 14, Figure S4: 13C-NMR (150 MHz, CDCl$_3$) of compound 14, Figure S5: 1H-NMR (600 MHz, CDCl$_3$) of compound 15, Figure S6: 13C-NMR (150 MHz, CDCl$_3$) of compound 15, Figure S7: 1H-NMR (600 MHz, CDCl$_3$) of compound 16, Figure S8: 13C-NMR (150 MHz, CDCl$_3$) of compound 16, Figure S9: 1H-NMR (600 MHz, CD$_2$OD-d$_4$) of compound 17, Figure S10: 1H-NMR (600 MHz, CD$_2$OD-d$_4$) of compound 17, Figure S11: 1H-NMR (600 MHz, CDCl$_3$) of compound 18, Figure S12: 13C-NMR (150 MHz, CDCl$_3$) of compound 18, Figure S13: 1H-NMR (600 MHz, CDCl$_3$) of compound 19, Figure S14: 13C-NMR (150 MHz, CDCl$_3$) of compound 19, Figure S15: 1H-NMR (600 MHz, CDCl$_3$) of compound 6, Figure S16: 13C-NMR (150 MHz, CDCl$_3$) of compound 6, Figure S17: 1H-NMR (600 MHz, CDCl$_3$) of compound 20, Figure S18: 13C-NMR (150 MHz, CDCl$_3$) of compound 20, Figure S19: 1H-NMR (600 MHz, CDCl$_3$) of compound 21, Figure S20: 13C-NMR (150 MHz, CDCl$_3$) of compound 21, Figure S21: 1H-NMR (600 MHz, CD$_2$OD-d$_4$) of compound 12, Figure S22: 13C-NMR (150 MHz, CD$_2$OD-d$_4$) of compound 12, Figure S23: 1H-NMR (600 MHz, CDCl$_3$) of compound 5, Figure S24: 13C-NMR (150 MHz, CDCl$_3$) of compound 5, Figure S25: 1H-NMR (600 MHz, CDCl$_3$) of compound 11, Figure S26: 13C-NMR (150 MHz, CDCl$_3$) of compound 11, Figure S27: 1H-NMR (600 MHz, CDCl$_3$) of compound 4, Figure S28: 13C-NMR (150 MHz, CDCl$_3$) of compound 4, Figure S29: 1H-NMR (600 MHz, CDCl$_3$) of compound 22, Figure S30: 13C-NMR (150 MHz, CDCl$_3$) of compound 22, Figure S31: 1H-NMR (600 MHz, (CD$_3$)$_2$CO) of compound 2, Figure S32: 13C-NMR (150 MHz, (CD$_3$)$_2$CO) of compound 2, Figure S33: 1H-NMR (600 MHz, CDCl$_3$) of compound 10, Figure S34: 13C-NMR (150 MHz, CDCl$_3$) of compound 10, Figure S35: 1H-NMR (600 MHz, CDCl$_3$) of Compound 23, Figure S36: 13C-NMR (150 MHz, CDCl$_3$) of Compound 23, Figure S37: 1H-NMR (600 MHz, CDCl$_3$) of compound 24, Figure S38: 13C-NMR (150 MHz, CDCl$_3$) of compound 24, Figure S39: 1H-NMR (600 MHz, (CD$_3$)$_2$CO) of compound 3, Figure S40: 13C-NMR (150 MHz, (CD$_3$)$_2$CO) of compound 3.

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