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Synthesis of Rosavin and its analogues based on a Mizoroki-Heck type reaction

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Abstract—The Rosavin framework could be constructed with either phenylboronic acids, the protected arabinopyranosyl bromide **4** or the protected xylopyranosyl bromide **5**, along with allyl *O*-β-D-glucopyranoside **7** that could be easily prepared based on direct β-glucosidation between allyl alcohol and D-glucose using the immobilized β-glucosidase (EC 3.2.1.21). The key reaction was the Pd(II)-catalyzed Mizoroki-Heck type reaction between allyl β-D-glucopyranoside congeners **9** or **10** and arylboronic acids. Deprotection of the coupling products afforded synthetic Rosavin **1**, 4-methoxycinnamyl 6-*O*-(α-L-arabinopyranosyl)-β-D-glucopyranoside **2**, and cinnamyl 6-*O*-(β-D-xylopyranosyl)-β-D-glucopyranoside **3**, which were identical with the natural products in respect to the specific rotation and spectral data.

1. Introduction

Golden root (Roseroot, *Rhodiola rosea* L., Crassulaceae) has been used for a long time as a resource in Chinese traditional medicine to enhance the body's resistance against fatigue and to extend human life.[1] Rosavin **1** was isolated as one of the chemical constituents of *R. rosea* by Kurkin et al.[2a,b] 4-Methoxycinnamyl 6-*O*-(α-L-arabinopyranosyl)-β-D-glucopyranoside **2** and cinnamyl 6-*O*-(β-D-xylopyranosyl)-β-D-glucopyranoside **3** were also isolated from an aqueous methanol extract of *R. rosea* by Ari et al.[2c] The synthesis of these three natural products has not yet been reported. Meanwhile, we have reported a simple total synthesis of cinnamyl β-glucopyranoside (Rosin) and its analogues using the Mizoroki-Heck (MH) type reaction between the substituted aryl boron reagents and allyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside using a Pd(II) catalyst as the key reaction.[3] The organoboron-mediated MH-type reaction with allyl phenyl ether via a Pd(II) species has been reported by Mori et al.[4] However, the reaction of allyl ether with phenyl boronic acid was examined in only one example in this literature, and our report was the first in which this methodology included a variety of phenylboronic acids having an electron-donating group, an electron-withdrawing group, or a non-protected hydroxyl group, and the total synthesis of natural products.[3] Herein, we report the first total synthesis of Rosavin **1** and its naturally occurring congeners **2** and **3** based on the Pd(II)-catalyzed MH-type reaction. The Rosavin framework was constructed from the protected arabinopyranosyl bromide **4** or the protected xylopyranosyl bromide **5** congener, the protected allyl β-D-glucoside **6**, and phenylboronic acid reagents (Scheme 1).

2. Results and discussion

The direct glucosidation of D-glucose using β-glucosidase (EC 3.2.1.21) from almonds has been reported by Crout.[5] Meanwhile, we have also reported the direct β-glucosidation between D-glucose and allyl alcohol using the immobilized β-glucosidase from almonds with the synthetic prepolymer ENTP-4000 to give the allyl β-D-glucopyranoside **7** in 68% yield.[3] The *tert*-butyldimethylsilyl (TBDMS) protection of the primary alcohol in **7** gave silyl ether **8** in 56% yield, which was subjected to consecutive benzoylation and deprotection of the TBDMS group to afford the desired allyl 2,3,4-tri-*O*-benzoyl-β-glucopyranoside **6** in 71% yield (two steps). On the other hand, 2,3,4-tri-*O*-benzoyl-β-L-arabinopyranosyl bromide[6] **4** and 2,3,4-tri-*O*-benzoyl-α-D-xylopyranosyl bromide[7] **5** were prepared by the reported procedures. *O*-Glycosylation of the alcohol **6** was

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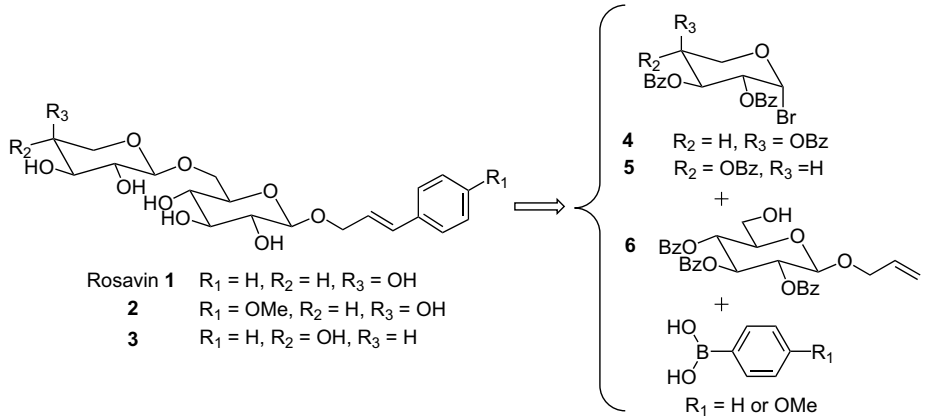
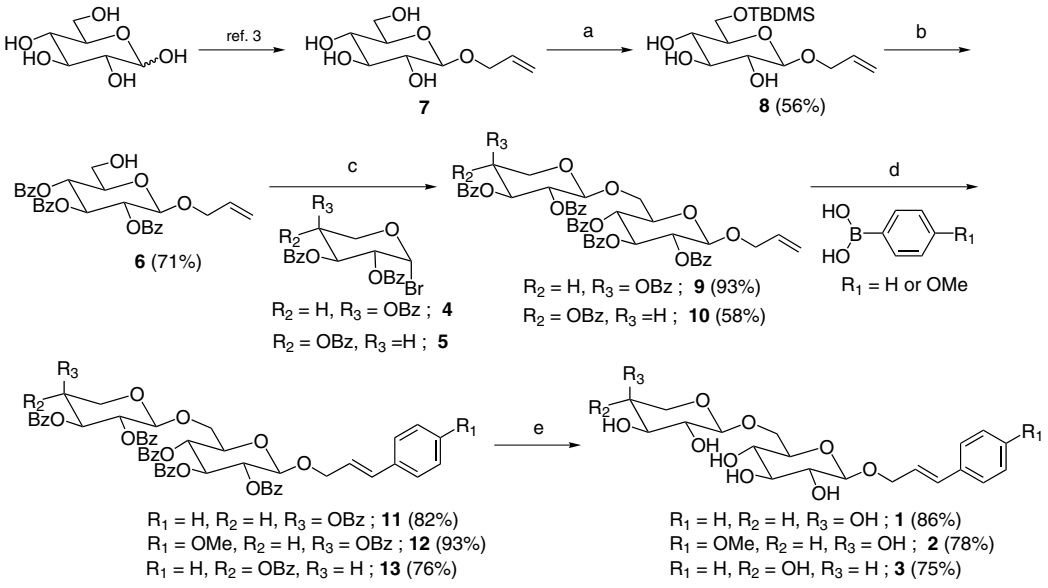


Scheme 1.



Scheme 2. Reagents and conditions: (a) TBDMSCl/pyridine/DMF, rt, 12 h; (b) (i) BzCl/pyridine, rt, overnight, (ii) 1 M HCl/THF, rt, 12 h; (c) **4** or **5**/AgOTf/tetramethylurea/CH_2Cl_2, 0 °C to rt, 12 h; (d) $PhB(OH)_2$ or 4-(MeO)$PhB(OH)_2$/cat. $Pd(OAc)_2$/$Cu(OAc)_2$/LiOAc/DMF, 100 °C, 1 h; (e) NaOMe/MeOH/THF, rt, 1 h.

carried out by the reported procedure.[8] Alcohol **6** was treated with 2 equiv of bromide **4** or **5** in the presence of silver triflate (AgOTf) and tetramethylurea (TMU) in CH_2Cl_2 at 0 °C to room temperature for 12 h to give the corresponding coupling products **9** or **10** in 85% and 66% yield, respectively. The coupling reaction of allyl ether **9** or **10** with phenylboronic acids was carried out using 10 mol % of $Pd(OAc)_2$, 2 equiv of $Cu(OAc)_2$, and 3 equiv of LiOAc in DMF at 100 °C for 1 h to afford the hexabenzoyl Rosavin **11** (82% yield) and its analogues **12** (93% yield) and **13** (76% yield), respectively. Finally, treatment of the coupling products **11**, **12**, and **13** with NaOMe in MeOH/THF provided the synthetic Rosavin **1**, 4-methoxycinnamyl 6-*O*-(α-L-arabinopyranosyl)-β-D-glucopyranoside **2** (86% yield), and cinnamyl 6-*O*-(β-D-xylopyranosyl)-β-D-glucopyranoside **3** (78% yield), respectively. The spectral data (^1H and ^{13}C NMR) and specific rotation {$[\alpha]_D^{27} = -54.7$ (*c* 0.70, $CHCl_3$–MeOH 1:1)} of the synthetic Rosavin **1** were identical with those {^1H NMR and $[\alpha]_D^{20} = -56.5$ (*c* 0.7, $CHCl_3$–MeOH 1:1)} of the natural product **1**.[2a,b] The spectral data (^1H and ^{13}C NMR) of the synthetic products **2** and **3** were also identical with those of natural products **2** and **3**, respectively (Scheme 2).[2c]

3. Conclusion

In conclusion, we have found that the Rosavin framework can be constructed with phenylboronic acids, the protected arabinopyranosyl bromide **4** or the protected xylopyranosyl bromide **5**, and an allyl *O*-β-D-glucopyranoside **7**, which can be easily prepared based on the direct β-glucosidation between allyl alcohol and D-glucose using the immobilized β-glucosidase. Based on this strategy, the coupling reaction of the protected allyl

β-D-glucopyranoside **6** and bromide **4** or **5** gave the coupled products **9** or **10**, respectively. The reaction of **9** or **10** with phenylboronic acid based on the Pd(II)-catalyzed MH-type reaction afforded the coupled products **11** or **13**, respectively. Moreover, the reaction of **9** with 4-methoxyphenylboronic acid based on the Pd(II)-catalyzed MH-type reaction provided the coupled product **12**. Deprotection of these coupled products **11**, **12**, and **13** gave the synthetic Rosavin **1** and its congeners **2** and **3**, respectively, which were consistent with the natural products with respect to the spectral data and specific rotations. By applying this strategy, structurally diverse Rosavin analogues can be easily prepared using a number of commercially available substituted phenylboronic acids, to investigate their biological activities.

4. Experimental

4.1. General

All melting points were measured on a Yanaco MP-3S micro melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on JEOL AL 400 spectrometer or Bruker 400 spectrometer in $CDCl_3$, methanol-d_4, D_2O, acetone-d_6, and pyridine-d_5 with Me_4Si as an internal reference. High-resolution mass spectra (HR-MS) and the fast atom bombardment mass spectra (FAB MS) were obtained with a JEOL JMS 600H spectrometer. IR spectra were recorded with a JASCO FT/IR-300 spectrometer. Specific rotations were measured with a JASCO DIP-370 digital polarimeter. All reagents were purchased from commercial sources and used without purification. All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed while for flash column chromatography, silica gel (Silica Gel 60N, spherical, neutral, 40–50 μm) was employed.

4.2. Allyl 6-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranoside 8

A mixture of **7**[3] (9.84 g, 45 mmol) and pyridine (4.27 g, 54 mmol) in DMF (90 mL) was treated with *tert*-butyldimethylsilyl chloride (TBDMSCl; 7.46 g, 49 mmol) dissolved in DMF (10 mL) at 0 °C and stirred at room temperature for 18 h. The reaction mixture was recooled at 0 °C and treated with pyridine (1.78 g, 23 mmol) and TBDMSCl (2.71 g, 18 mmol). After being stirred at 0–5 °C for 20 min, the reaction mixture was diluted with 0.2 M aqueous HCl (100 mL) and extracted with AcOEt. The organic layer was washed with water (100 mL), saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was purified by flash column chromatography on silica gel [200 g, CH_2Cl_2/MeOH (20:1–15:1)] to afford **8** (8.30 g, 56%) as a colorless prism. Mp 84.5–86.5 °C (CH_2Cl_2/MeOH); $[\alpha]_D^{27} = -45.9$ (*c* 0.75, $CHCl_3$); IR (KBr) 3398, 2929, 2856, 1252, 1144, 1113, 1058, 837, 776 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.83 (dddd, 1H, $J = 5.0$, 6.6, 10.4, 17.2 Hz), 5.21 (tdd, 1H, $J = 1.5$, 1.5, 17.2 Hz), 5.12 (tdd, 1H, $J = 1.2$, 1.5, 10.4 Hz), 4.25 (tdd, 1H, $J = 1.5$, 5.3, 12.6 Hz), 4.24 (d, 1H, $J = 7.6$ Hz), 4.01 (tdd, 1H, $J = 1.2$, 6.6, 12.6 Hz), 3.84 (dd, 1H, $J = 5.0$, 10.4 Hz), 3.74 (dd, 1H, $J = 6.6$, 10.4 Hz), 3.51–3.46 (m, 2H), 3.34–3.25 (m, 3H), 2.70 (d, 1H, $J = 1.8$ Hz), 2.41 (d, 1H, $J = 2.3$ Hz), 0.80 (s, 9H), 0.0036 (s, 3H), −0.0002 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 133.8, 118.0, 101.3, 76.3, 74.8, 73.4, 72.2, 70.1, 64.3, 25.8, 18.2, −5,4; Anal. Calcd for $C_{15}H_{30}O_6Si$: C, 53.44; H, 8.84. Found: C, 53.86; H, 9.04.

4.3. Allyl 2,3,4-tri-*O*-benzoyl-β-D-glucopyranoside 6

A mixture of **8** (0.46 g, 1.4 mmol) and benzoyl chloride (0.97 g, 6.9 mmol) in pyridine (4.0 mL) was stirred at room temperature for 18 h. The reaction mixture was diluted with 1 M HCl and extracted with AcOEt. The organic layer was washed with 1 M aqueous HCl, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, and evaporated to give a crude allyl 2,3,4-*tri*-*O*-benzoyl-6-*tert*-butyldimethylsilyl-β-D-glycopyranoside. The crude product was treated with 1 M aqueous HCl (1.5 mL) in THF (5 mL) and stirred at room temperature for 12 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give a residue, which was purified by flash column chromatography on silica gel [30 g, *n*-hexane/AcOEt (3:1–1:1)] to afford **6** (0.52 g, 71%) as a colorless prism. Mp 114.0–115.8 °C (*n*-hexane/AcOEt); $[\alpha]_D^{27} = -0.7$ (*c* 0.54, $CHCl_3$); IR (KBr) 3372, 2952, 1729, 1601, 1452, 1373, 1261, 1175, 1072, 710 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.97–7.93 (m, 4H), 7.85–7.83 (m, 2H), 7.54–7.48 (m, 2H), 7.43–7.35 (m, 5H), 7.29–7.25 (m, 2H), 5.94 (t, 1H, $J = 9.6$ Hz), 5.81 (dddd, 1H, $J = 4.8$, 6.3, 10.6, 17.4 Hz), 5.55 (dd, 1H, $J = 8.1$, 9.6 Hz), 5.51 (t, 1H, $J = 9.6$ Hz), 5.25 (dddd, 1H, $J = 1.2$, 1.5, 3.3, 17.4 Hz), 5.14 (dddd, 1H, $J = 1.2$, 1.5, 3.3, 10.6 Hz), 4.90 (d, 1H, $J = 8.1$ Hz), 4.39 (tdd, 1H, $J = 1.5$, 4.8, 13.1 Hz), 4.19 (tdd, 1H, $J = 1.2$, 6.3, 13.1 Hz), 3.89–3.74 (m, 3H), 2.62 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.0, 165.8, 165.0, 133.6, 133.4, 133.20, 133.15, 129.9 (2C), 129.73 (2C), 129.69 (2C), 129.3, 128.8, 128.6, 128.5 (2C), 128.30 (2C), 128.25 (2C), 117.7, 99.9, 74.6, 72.8, 71.8, 70.2, 69.6, 61.3; Anal. Calcd for $C_{30}H_{28}O_9$: C, 67.55; H, 5.32. Found: C, 67.66; H, 5.30.

4.4. Allyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4-tri-*O*-benzoyl-α-L-arabinopyranosyl)-β-D-glucopyranoside 9

A 50-mL three-necked round-bottom flask covered with aluminum foil, was charged with **6** (1.33 g, 2.5 mmol), 2,3,4-tri-*O*-benzoyl-β-L-arabinopyranosyl bromide **4**[6] (2.63 g, 5.0 mmol), tetramethylurea (0.87 g, 7.5 mmol), and CH_2Cl_2 (10 mL). To this solution was added AgOTf (1.28 g, 5.0 mmol) at 0 °C under an argon atmosphere and stirred for 12 h at room temperature. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel [90 g, *n*-hexane/AcOEt

(4:1–2:1)] to afford **9** with a by-product, which was recrystallized from acetone/*n*-hexane to give pure **9** (2.07 g, 85%) as a white powder. Mp 197.0–198.2 °C; $[\alpha]_D^{27} = -72.9$ (*c* 0.62, $CHCl_3$); IR (KBr) 1725, 1453, 1260, 1095, 1029, 712 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.03–8.00 (m, 4H), 7.94–7.87 (m, 6H), 7.78–7.76 (m, 2H), 7.59–7.54 (m, 1H), 7.53–7.47 (m, 4H), 7.45–7.33 (m, 11H), 7.28–7.24 (m, 2H), 5.82 (t, 1H, $J = 9.6$ Hz), 5.74 (dd, 1H, $J = 6.3$, 8.6 Hz), 5.68–5.65 (m, 1H), 5.61 (dd, 1H, $J = 3.0$, 8.8 Hz), 5.55 (dddd, 1H, $J = 4.8$, 6.3, 10.6, 17.2 Hz), 5.42 (dd, 1H, $J = 8.1$, 9.8 Hz), 5.37 (t, 1H, $J = 9.6$ Hz), 5.09 (dddd, 1H, $J = 1.2$, 1.5, 3.3, 17.2 Hz), 5.03 (dddd, 1H, $J = 1.2$, 1.5, 3.3, 10.6 Hz), 4.84 (d, 1H, $J = 6.3$ Hz), 4.72 (d, 1H, $J = 7.8$ Hz), 4.27 (dd, 1H, $J = 4.0$, 12.8 Hz), 4.09 (dd, 1H, $J = 1.8$, 11.1 Hz), 4.04–3.97 (m, 2H), 3.86 (dd, 1H, $J = 2.2$, 12.9 Hz), 3.84–3.77 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.7, 165.6, 165.5, 165.3, 165.2, 165.0, 133.5, 133.4 (3C), 133.15, 133.11, 133.0, 129.85 (2C), 129.81 (6C), 129.72 (2C), 129.69 (2C), 129.35, 129.31, 129.2, 129.0, 128.8, 128.7, 128.46 (2C), 128.45 (2C), 128.41 (2C), 128.40 (2C), 128.3 (2C), 128.2 (2C), 117.5, 100.9, 99.5, 73.8, 72.9, 71.8, 70.4, 69.81, 69.75, 69.4, 68.4, 68.3, 62.5; Anal. Calcd for $C_{56}H_{48}O_{16}$: C, 68.85; H, 4.95. Found: C, 68.86; H, 5.04.

4.5. Allyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4-tri-*O*-benzoyl-β-D-xylopyranosyl)-β-D-glucopyranoside 10

A 50-mL three-necked round-bottom flask covered with aluminum foil was charged with **6** (1.05 g, 2.0 mmol), 2,3,4-tri-*O*-benzoyl-α-D-xylopyranosyl bromide **5**[7] (2.09 g, 4.0 mmol), tetramethylurea (0.69 g, 6.0 mmol), and CH_2Cl_2 (8.0 mL). To this solution was added AgOTf (1.02 g, 4.0 mmol) at 0 °C under an argon atmosphere and stirred for 12 h at room temperature. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel [100 g, *n*-hexane/AcOEt (4:1–2:1)] to afford **10** with a by-product, which was recrystallized from acetone/*n*-hexane to afford a pure **10** (1.29 g, 67%) as a white powder. Mp 196.8–197.3 °C; $[\alpha]_D^{27} = -24.9$ (*c* 0.51, $CHCl_3$); IR (KBr) 1729, 1261, 1177, 1101, 1029, 710 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.05–7.96 (m, 6H), 7.94–7.89 (m, 4H), 7.79–7.76 (m, 2H), 7.55–7.47 (m, 5H), 7.42–7.31 (m, 11H), 7.27–7.23 (m, 2H), 5.84 (t, 1H, $J = 9.6$ Hz), 5.76 (t, 1H, $J = 7.3$ Hz), 5.61 (dddd, 1H, $J = 4.5$, 6.1, 10.4, 17.4 Hz), 5.46 (dd, 1H, $J = 8.1$, 9.6 Hz), 5.42 (t, 1H, $J = 9.6$ Hz), 5.40 (dd, 1H, $J = 5.3$, 7.3 Hz), 5.26 (dt, 1H, $J = 4.3$, 7.3 Hz), 5.14 (tdd, 1H, $J = 1.5$, 3.3, 17.4 Hz), 5.06 (tdd, 1H, $J = 1.5$, 3.3, 10.4 Hz), 4.91 (d, 1H, $J = 5.3$ Hz), 4.75 (d, 1H, $J = 8.1$ Hz), 4.40 (dd, 1H, $J = 4.3$, 12.1 Hz), 4.10 (tdd, 1H, $J = 1.5$, 4.5, 13.4 Hz), 4.08–3.99 (m, 2H), 3.88 (tdd, 1H, $J = 1.5$, 6.1, 13.4 Hz), 3.81 (dd, 1H, $J = 7.0$, 11.4 Hz), 3.68 (dd, 1H, $J = 7.3$, 12.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.7, 165.5, 165.4, 165.3, 165.03, 165.00, 133.5, 133.38, 133.35, 133.3, 133.14, 133.11, 133.07, 129.9 (4C), 129.8 (4C), 129.73 (2C), 129.71 (2C), 129.3, 129.22, 129.16, 129.1, 128.8, 128.7, 128.5 (2C), 128.42 (2C), 128.38 (2C), 128.36 (2C), 128.3 (2C), 128.2 (2C), 117.5, 100.4, 99.7, 73.8, 72.9, 71.9, 70.2 (2C), 69.7, 69.6, 69.1, 68.0, 61.2; Anal. Calcd for $C_{56}H_{48}O_{16}$: C, 68.83; H, 5.00. Found: C, 68.85; H, 4.95.

4.6. Cinnamyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4-tri-*O*-benzoyl-α-L-arabinopyranosyl)-β-D-glucopyranoside 11

A mixture of **9** (0.489 g, 0.50 mmol), phenylboronic acid (0.073 g, 0.60 mmol), copper(II) acetate (0.182 g, 1.0 mmol), lithium acetate (0.099 g, 1.5 mmol), and palladium(II) acetate (0.0112 g, 0.050 mmol) in DMF (2.0 mL) was stirred for 1 h at 100 °C. This was allowed to cool to room temperature and the reaction mixture diluted with EtOAc and water. The organic layer was washed with 1 M aqueous HCl and brine, dried over $MgSO_4$, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel [25 g, *n*-hexane/AcOEt (3:1–3:2)] to afford **11** (0.438 g, 82%) as a white solid. The white solid was recrystallized from ether to give **11** (0.274 g, 52%), a pure white solid to be analyzed by microanalyses. Mp 182.0–184.0 °C; $[\alpha]_D^{27} = +51.8$ (*c* 0.50, $CHCl_3$); IR (KBr) 1730, 1454, 1260, 1093, 710 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.04–8.01 (m, 4H), 7.94–7.91 (m, 4H), 7.90–7.87 (m, 2H), 7.79–7.76 (m, 2H), 7.58–7.54 (m, 1H), 7.53–7.46 (m, 4H), 7.43–7.32 (m, 11H), 7.28–7.22 (m, 5H), 7.16–7.13 (m, 2H), 6.36 (d, 1H, $J = 15.9$ Hz), 5.87 (ddd, 1H, $J = 4.8$, 6.6, 15.9 Hz), 5.82 (t, 1H, $J = 9.8$ Hz), 5.76 (dd, 1H, $J = 6.6$, 8.8 Hz), 5.66 (ddd, 1H, $J = 2.0$, 3.6, 4.0 Hz), 5.61 (dd, 1H, $J = 3.6$, 8.8 Hz), 5,45 (dd, 1H, $J = 8.1$, 9.8 Hz), 5.38 (t, 1H, $J = 9.8$ Hz), 4.85 (d, 1H, $J = 6.3$ Hz), 4.76 (d, 1H, $J = 8.1$ Hz), 4.27 (dd, 1H, $J = 4.0$, 13.1 Hz), 4.15–4.00 (m, 2H), 4.05–4.00 (m, 1H), 3.93 (ddd, 1H, $J = 1.0$, 6.9, 13.8 Hz), 3.87–3.82 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.7, 165.6, 165.5, 165.4, 165.2, 165.0, 136.3, 133.5, 133.4 (3C), 133.15, 133.13, 132.7, 129.9 (4C), 129.8 (8C), 129.7 (2C), 129.4, 129.3, 129.2, 129.0, 128.8, 128.7, 128.49 (2C), 128.45 (4C), 128.4 (2C), 128.3 (2C), 128.2 (2C), 127.7, 126.4 (2C), 124.2, 101.0, 99.4, 73.8, 72.9, 71.9, 70.4, 69.9, 69.8, 69.1, 68.5, 68.4, 62.6; Anal. Calcd for $C_{62}H_{52}O_{16}$: C, 70.71; H, 4.98. Found: C, 70.37; H, 5.04.

4.7. 4-Methoxycinnamyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4-tri-*O*-benzoyl-α-L-arabinopyranosyl)-β-D-glucopyranoside 12

A mixture of **9** (0.489 g, 0.50 mmol), 4-methoxyphenylboronic acid (0.091 g, 0.60 mmol), copper(II) acetate (0.182 g, 1.0 mmol), lithium acetate (0.099 g, 1.5 mmol), and palladium(II) acetate (0.0112 g, 0.050 mmol) in DMF (2.0 mL) was stirred for 1 h at 100 °C. This was allowed to cool to room temperature and the reaction mixture diluted with EtOAc and water. The organic layer was washed with 1 M aqueous HCl and brine, dried over $MgSO_4$, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel [25 g, *n*-hexane/AcOEt (3:1–3:2)] to afford **12** (0.506 g, 93%) as a white solid. The white solid was recrystallized from acetone to provide **12** (0.137 g, 25%), a pure white solid to be analyzed by

microanalyses. Mp 192.2–193.7 °C; $[\alpha]_D^{27} = +54.6$ (*c* 0.28, $CHCl_3$); IR (KBr) 1732, 1604, 1512, 1452, 1257, 1176, 1094, 1029, 710 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.04–8.01 (m, 4H), 7.95–7.91 (m, 4H), 7.90–7.87 (m, 2H), 7.79–7.76 (m, 2H), 7.58–7.54 (m, 1H), 7.53–7.46 (m, 4H), 7.43–7.32 (m, 11H), 7.28–7.23 (m, 2H), 7.10 (d, 2H, $J = 8.6$ Hz), 6.79 (d, 2H, $J = 8.6$ Hz), 6.30 (d, 1H, $J = 15.9$ Hz), 5.81 (t, 1H, $J = 9.6$ Hz), 5.76 (dd, 1H, $J = 6.3$, 8.6 Hz), 5.74 (ddd, 1H, $J = 5.0$, 7.0, 15.9 Hz), 5.66 (ddd, 1H, $J = 1.8$, 3.6, 4.0 Hz), 5.61 (dd, 1H, $J = 3.6$, 8.6 Hz), 5.44 (dd, 1H, $J = 8.1$, 9.6 Hz), 5.38 (dd, 1H, $J = 9.6$, 9.8 Hz), 4.84 (d, 1H, $J = 6.3$ Hz), 4.76 (d, 1H, $J = 8.1$ Hz), 4.27 (dd, 1H, $J = 4.0$, 12.9 Hz), 4.13–4.08 (m, 2H), 4.03 (dt, 1H, $J = 3.8$, 9.6 Hz), 3.91 (dd, 1H, $J = 7.1$, 14.2 Hz), 3.87–3.82 (m, 2H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.7, 165.6, 165.5, 165.4, 165.2, 165.0, 159.3, 133.5, 133.4 (3C), 133.14, 133.10, 132.6, 129.9 (2C), 129.8 (8C), 129.7 (2C), 129.4 (2C), 129.2, 129.1, 129.0, 128.8, 128.7, 128.49 (2C), 128.46 (2C), 128.4 (4C), 128.3 (2C), 128.2 (2C), 127.7 (2C), 121.9, 113.9 (2C), 101.0, 99.3, 73.8, 73.0, 71.9, 70.4, 69.9, 69.8, 69.3, 68.5, 68.4, 62.6, 55.3; Anal. Calcd for $C_{63}H_{54}O_{17}$: C, 69.86; H, 5.03. Found: C, 69.79; H, 5.08.

4.8. Cinnamyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4-tri-*O*-benzoyl-β-D-xylopyranosyl)-β-D-glucopyranoside 13

A mixture of **10** (0.489 g, 0.50 mmol), phenylboronic acid (0.073 g, 0.60 mmol), copper(II) acetate (0.182 g, 1.0 mmol), lithium acetate (0.099 g, 1.5 mmol), and palladium(II) acetate (0.0112 g, 0.050 mmol) in DMF (2.0 mL) was stirred for 1 h at 100 °C. This was allowed to cool to room temperature and the reaction mixture was diluted with EtOAc and water. The organic layer was washed with 1 M aqueous HCl and brine, dried over $MgSO_4$, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel [30 g, *n*-hexane/AcOEt (4:1–2:1)] to afford **13** (0.403 g, 76%) as a colorless solid. The white solid was recrystallized from acetone/*n*-hexane to give **13** (0.326 g, 62%) as a pure white powder. Mp 183.2–185.0 °C; $[\alpha]_D^{27} = -35.3$ (*c* 0.53, $CHCl_3$); IR (KBr) 1730, 1453, 1260, 1177, 1098, 1027, 710 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.01–7.97 (m, 6H), 7.95–7.93 (m, 2H), 7.92–7.89 (m, 2H), 7.79–7.76 (m, 2H), 7.55–7.47 (m, 5H), 7.42–7.16 (m, 18H), 6.41 (d, 1H, $J = 16.2$ Hz), 5.94 (ddd, 1H, $J = 5.0$, 6.6, 16.2 Hz), 5.84 (t, 1H, $J = 9.6$ Hz), 5.77 (t, 1H, $J = 7.3$ Hz), 5.47 (dd, 1H, $J = 7.8$, 9.6 Hz), 5.43 (t, 1H, $J = 9.6$ Hz), 5.43 (dd, 1H, $J = 5.6$, 7.3 Hz), 5.27 (dt, 1H, $J = 4.3$, 7.3 Hz), 4.92 (d, 1H, $J = 5.6$ Hz), 4.80 (d, 1H, $J = 7.8$ Hz), 4.39 (dd, 1H, $J = 4.3$, 12.1 Hz), 4.23 (ddd, 1H, $J = 1.5$, 4.8, 13.4 Hz), 4.08–4.00 (m, 3H), 3.82 (dd, 1H, $J = 7.1$, 11.1 Hz), 3.66 (dd, 1H, $J = 7.3$, 12.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.7, 165.5, 165.4, 165.3, 165.1, 165.0, 136.3, 133.5, 133.38, 133.35, 133.3, 133.1 (2C), 132.8, 129.9 (4C), 129.84 (4C), 129.81 (2C), 129.7 (2C), 129.3, 129.23, 129.16, 129.1, 128.8, 128.7, 128.5 (4C), 128.43 (2C), 128.39 (4C), 128.35 (2C), 128.2 (2C), 127.7, 126.5 (2C), 124.3, 100.5, 99.6, 73.9, 72.9, 71.9, 70.3 (2C), 69.7, 69.3, 69.1, 68.1, 61.3; High (FAB)-MS *m/z*: 1053.3364. Calcd for $C_{62}H_{53}O_{16}$: 1053.3333 $(M+1)^+$.

4.9. Cinnamyl 6-*O*-(α-L-arabinopyranosyl)-β-D-glucopyranoside 1 (Rosavin)

To a solution of **11** (0.2630 g, 0.25 mmol) in 4 mL of methanol/THF (1:1) was added a solution of 25% NaOMe in MeOH (0.062 g, 0.30 mmol). The whole mixture was stirred for 1 h. A small amount of ion exchange resin (Amberlyst 15, H^+-form) was added to the reaction mixture to remove sodium ions. The reaction mixture was diluted with methanol and the resin filtered off. The filtrate was evaporated with silica gel (1.0 g) to dryness and the residue purified by flash chromatography on silica gel [4 g, CH_2Cl_2/MeOH (9:1–5:1)] to afford **1** (0.0923 g, 86%) as a colorless amorphous solid. Mp 97.0–99.0 °C (MeOH);[9] $[\alpha]_D^{27} = -54.7$ (*c* 0.70, $CHCl_3$–MeOH 1:1) {lit.[2a,b] $[\alpha]_D^{20} = -56.5$ (*c* 0.7, $CHCl_3$–MeOH 1:1)}; IR (KBr) 3390, 2881, 1368, 1077, 745, 694, 644 cm^{-1}; ^1H NMR (pyridine-d_5, 400 MHz) δ: 7.43–7.40 (m, 2H), 7.32–7.28 (m, 2H), 7.24–7.21 (m, 1H), 6.82 (d, 1H, $J = 15.9$ Hz), 6.48 (td, 1H, $J = 6.1$, 15.9 Hz), 4.98 (d, 1H, $J = 6.8$ Hz), 4.92 (d, 1H, $J = 7.6$ Hz), 4.88 (dd, 1H, $J = 2.0$, 11.1 Hz), 4.79 (ddd, 1H, $J = 1.5$, 5.6, 13.1 Hz), 4.51 (dd, 1H, $J = 6.8$, 8.6 Hz), 4.47 (ddd, 1H, $J = 1.3$, 6.3, 13.2 Hz), 4.36–4.30 (m, 3H), 4.23 (dd, 1H, $J = 8.6$, 8.6 Hz), 4.20–4.15 (m, 2H), 4.12–4.07 (m, 1H), 4.07 (dd, 1H, $J = 8.3$, 8.3 Hz), 3.76 (dd, 1H, $J = 2.5$, 12.9 Hz); ^1H NMR (methanol-d_4, 400 MHz) δ: 7.42 (d, 2H, $J = 7.6$ Hz), 7.30 (t, 2H, $J = 7.6$ Hz), 7.21 (t, 1H, $J = 7.1$ Hz), 6.69 (d, 1H, $J = 15.9$ Hz), 6.36 (td, 1H, $J = 6.0$, 15.9 Hz), 4.51 (dd, 1H, $J = 5.6$, 13.1 Hz), 4.37 (d, 1H, $J = 7.8$ Hz), 4.33 (d, 1H, $J = 6.8$ Hz), 4.35–4.29 (m, 1H), 4.11 (d, 1H, $J = 10.9$ Hz), 3.86 (dd, 1H, $J = 3.0$, 12.4 Hz), 3.78–3.76 (m, 1H), 3.74 (dd, 1H, $J = 5.8$, 11.4 Hz), 3.61 (t, 1H, $J = 7.1$ Hz), 3.54–3.50 (m, 2H), 3.46–3.44 (m, 1H), 3.37–3.33 (m, 2H), 3.24 (t, 1H, $J = 7.6$ Hz); ^{13}C NMR (methanol-d_4, 100 MHz) δ: 138.2 (C-4), 133.7 (C-3), 129.6 (C-6 and C-8), 128.7 (C-7), 127.5 (C-5 and C-9), 126.7 (C-2), 105.2 (C″-1), 103.4 (C′-1), 78.0 (C′-3), 76.9 (C′-5), 75.1 (C′-2), 74.2 (C″-3), 72.4 (C″-2), 71.7 (C′-4), 70.9 (C-1), 69.51 (C′-6 or C″-4), 69.49 (C″-4 or C′-6), 66.7 (C″-5); High (FAB)-MS *m/z*: 429.1755. Calcd for $C_{20}H_{29}O_{10}$: 429.1761 $(M+1)^+$.

4.10. 4-Methoxycinnamyl 6-*O*-(α-L-arabinopyranosyl)-β-D-glucopyranoside 2

To a solution of compound **12** (0.1100 g, 0.10 mmol) in 6 mL of methanol/THF (1:2) was added a solution of 25% NaOMe in MeOH (0.040 g, 0.20 mmol). The whole mixture was stirred for 1 h. A small amount of ion exchange resin (Amberlyst 15, H^+-form) was added to the reaction mixture to remove the sodium ions. The reaction mixture was diluted with methanol and the resin filtered off. The filtrate was evaporated with silica gel (0.50 g) to dryness and the residue was purified by flash chromatography on silica gel [4 g, CH_2Cl_2/MeOH (9:1–5:1)] to provide **2** (0.0355 g, 78%) as a colorless amorphous crystal. Mp 99.5–101.0 °C (MeOH); $[\alpha]_D^{25} = -46.6$ (*c* 0.31, MeOH); IR (KBr) 3751, 3400, 2910, 1606, 1513, 1251, 1042 cm^{-1}; ^1H NMR (D_2O, 400 MHz) δ: 7.39 (d, 2H, $J = 8.6$ Hz), 6.62 (d, 2H,

$J = 8.6$ Hz), 6.62 (d, 1H, $J = 15.9$ Hz), 6.21 (td, 1H, $J = 6.8$, 15.9 Hz), 4.46 (d, 1H, $J = 7.8$ Hz), 4.42 (dd, 1H, $J = 6.3$, 12.9 Hz), 4.31 (dd, 1H, $J = 7.1$, 12.9 Hz), 4.30 (d, 1H, $J = 7.3$ Hz), 4.06 (dd, 1H, $J = 1.5$, 11.6 Hz), 3.85–3.79 (m, 2H), 3.76 (s, 3H), 3.75 (dd, 1H, $J = 5.3$, 11.4 Hz), 3.58–3.47 (m, 4H), 3.43–3.37 (m, 2H), 3.26–3.21 (m, 1H); ^{1}H NMR (methanol-d_4, 400 MHz) δ: 7.35 (d, 2H, $J = 8.6$ Hz), 6.86 (d, 2H, $J = 8.6$ Hz), 6.62 (d, 1H, $J = 15.9$ Hz), 6.21 (td, 1H, $J = 6.8$, 15.9 Hz), 4.48 (ddd, 1H, $J = 1.3$, 5.8, 12.6 Hz), 4.36 (d, 1H, $J = 7.8$ Hz), 4.33 (d, 1H, $J = 6.8$ Hz), 4.29 (ddd, 1H, $J = 1.0$, 7.8, 12.6 Hz), 3.86 (dd, 1H, $J = 3.0$, 12.4 Hz), 3.82–3.78 (m, 1H), 3.78 (s, 3H), 3.74 (dd, 1H, $J = 5.8$, 11.4 Hz), 3.61 (dd, 1H, $J = 6.8$, 8.8 Hz), 3.55–3.51 (m, 2H), 3.46–3.40 (m, 1H), 3.37–3.33 (m, 3H), 3.25–3.20 (m, 1H); ^{13}C NMR (D_2O, 100 MHz) δ: 159.2 (C-7), 133.6 (C-3), 129.9 (C-4), 128.4 (C-5 and C-9), 123.2 (C-2), 114.7 (C-6 and C-8), 104.0 (C″-1), 101.6 (C′-1), 76.1 (C′-3), 75.3 (C′-5), 73.4 (C′-2), 72.6 (C″-3), 71.04 (C-1), 70.98 (C″-2), 69.7 (C′-4), 68.65 (C′-6), 68.58 (C″-4), 66.5 (C″-5), 55.7 (OMe); ^{13}C NMR (methanol-d_4, 100 MHz) δ: 160.9 (C-7), 133.7 (C-3), 130.9 (C-4), 128.8 (C-5 and C-9), 124.3 (C-2), 115.0 (C-6 and C-8), 105.2 (C″-1), 103.3 (C′-1), 78.0 (C′-3), 76.9 (C′-5), 75.1 (C′-2), 74.2 (C″-3), 72.4 (C″-2), 71.7 (C′-4), 71.1 (C-1), 69.5 (C′-6 and C″-4), 66.7 (C″-5), 55.7 (OMe); High (FAB)-MS m/z; 459.1823. Calcd for $C_{21}H_{31}O_{11}$: 459.1867 $(M+1)^+$.

4.11. Cinnamyl 6-*O*-(β-D-xylopyranosyl)-β-D-glucopyranoside 3

To a solution of **13** (0.2100 g, 0.20 mmol) in 4 mL of methanol/THF (1:1) was added a solution of 25% NaOMe in MeOH (0.072 g, 0.29 mmol). The whole mixture was stirred for 30 min. A small amount of ion exchange resin (Amberlyst 15, H^+-form) was added to the reaction mixture to remove sodium ions. The reaction mixture was diluted with methanol and the resin filtered off. The filtrate was evaporated with silica gel (1.0 g) to dryness and the residue purified by flash chromatography on silica gel [4 g, CH_2Cl_2/MeOH (9:1–5:1)] to provide **3** (0.0642 g, 75%) as a colorless amorphous crystal. Mp 177.0–178.5 °C (CH_2Cl_2/MeOH); $[\alpha]_D^{24} = -71.9$ (*c* 0.40, MeOH); IR (KBr) 3394, 2880, 1367, 1167, 1041, 743, 693, 623 cm^{-1}; ^{1}H NMR (D_2O, 400 MHz) δ: 7.43 (dd, 2H, $J = 1.2$, 8.6 Hz), 7.32 (dd, 2H, $J = 7.1$, 8.6 Hz), 7.25 (t, 1H, $J = 1.2$, 7.1 Hz), 6.66 (d, 1H, $J = 15.9$ Hz), 6.31 (td, 1H, $J = 6.6$, 15.9 Hz), 4.45 (d, 1H, $J = 7.8$ Hz), 4.43 (ddd, 1H, $J = 1.3$, 6.1, 12.9 Hz), 4.33 (d, 1H, $J = 7.6$ Hz), 4.33 (ddd, 1H, $J = 1.0$, 5.6, 12.9 Hz), 4.03 (dd, 1H, $J = 1.0$, 11.6 Hz), 3.83 (dd, 1H, $J = 5.6$, 11.6 Hz), 3.74 (dd, 1H, $J = 5.8$, 11.6 Hz), 3.54–3.45 (m, 2H), 3.41–3.35 (m, 2H), 3.33 (t, 1H, $J = 9.1$), 3.24–3.16 (m, 3H); ^{1}H NMR (methanol-d_4, 400 MHz) δ: 7.42 (d, 2H, $J = 7.6$ Hz), 7.30 (t, 2H, $J = 7.6$ Hz), 7.21 (t, 1H, $J = 7.1$ Hz), 6.70 (d, 1H, $J = 15.9$ Hz), 6.36 (td, 1H, $J = 6.3$, 15.9 Hz), 4.52 (ddd, 1H, $J = 1.2$, 5.8, 12.9 Hz), 4.36 (d, 1H, $J = 8.8$ Hz), 4.34 (d, 1H, $J = 7.6$ Hz), 4.33 (dd, 1H, $J = 6.1$, 12.9 Hz), 4.10 (dd, 1H, $J = 2.0$, 11.6 Hz), 3.86 (dd, 1H, $J = 5.3$, 11.4 Hz), 3.75 (dd, 1H, $J = 5.8$, 11.4 Hz), 3.52–3.43 (m, 2H), 3.38–3.30 (m, 3H), 3.27–3.16 (m, 3H); ^{13}C NMR (D_2O, 100 MHz) δ: 136.7 (C-4), 134.0 (C-3), 129.2 (C-6 and C-8), 128.5 (C-7), 126.9 (C-5 and C-9), 125.2 (C-2), 103.9 (C″-1), 101.5 (C′-1), 76.0 (C″-3), 75.9 (C′-3), 75.1 (C′-5), 73.4 (C′-2), 73.2 (C″-2), 70.8 (C-1), 69.7 (C′-4), 69.5 (C″-4), 68.9 (C′-6), 65.4 (C″-5); ^{13}C NMR (methanol-d_4, 100 MHz) δ: 138.3 (C-4), 133.9 (C-3), 129.6 (C-6 and C-8), 128.7 (C-7), 127.6 (C-5 and C-9), 126.7 (C-2), 105.6 (C″-1), 103.4 (C′-1), 78.0 (C″-3 or C′-3), 77.8 (C′-3 or C″-3), 77.0 (C′-5), 75.1 (C″-2 or C′-2), 74.9 (C′-2 or C″-2), 71.5 (C′-4), 71.2 (C″-4), 70.9 (C-1), 69.8 (C′-6), 67.0 (C″-5); High (FAB)-MS m/z: 429.1761. Calcd for $C_{20}H_{29}O_{10}$: 429.1761 $(M+1)^+$.

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