A Short Synthesis of Rhaponticin and its 3''-Fluoroanalog *via* a Wittig/Heck-Mizoroki Route

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Rhaponticin and its 3''-fluoroanalog have been prepared from easily accessible starting materials. The key step of these syntheses is the silver carbonate-mediated glycosidation reaction employed for the selective formation of a β-glycosidic bond. A palladium acetate-catalyzed Heck-Mizoroki reaction in triethanolamine established an (*E*) configuration in the stilbene with simultaneous deprotection of the carbohydrate.

Key words: Rhaponticin, Heck-Mizoroki Reaction, Fluorination

Introduction

Rhaponticin (**1**, Fig. 1) is a naturally occurring stilbene glucoside known for its estrogenic effects. Among others, extracts from the plant *rheum rhaponticum* ("rhubarb") [1, 2] containing significant amounts of **1** are used as alternative cures [3, 4] to the classical hormone replacement therapy mitigating the side effects often associated with the female menopause, *e. g.* headache and dizziness. Typically, pure samples of **1** are gained from its natural sources, *e. g.* species of *rheum* [5, 6], *eucalyptus* [7] or *guibourtia* [8].

Interestingly enough, although **1** has been used in Traditional Chinese Medicine (TCM) [1, 2] for more than 5000 years, and its isolation and structure [9, 10] have been known for several decades, no total synthesis of **1** has been described as yet. Recently, stilbenes came in the focus of scientific interest because of their antitumor activity [11] through antiangiogenic action [12], and as neuroprotectants [13, 14].

Results and Discussion

Retrosynthetic analysis of **1** revealed 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**2**) as an easily accessible starting material for the synthesis of **1**. Although stilbenes can be obtained [15] by Wittig and Wittig-Horner reactions, Peterson olefinations, aldol-type condensations, Negishi-Stille as well as by Barton-Kellog-Staudinger reactions, Siergrist's method, or McMurry coupling reactions, the use of a Heck-Mizoroki reaction to make the (*E*) configurated stilbene seemed most promising.

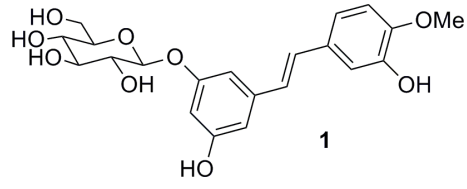

Fig. 1. Structure of rhaponticin (**1**).

Thus, commercially available 3,5-dimethoxyaniline (**3**) was transformed *in situ* [16, 17] into the diazonium salt (Scheme 1); its reaction with KI yielded the iodo compound **4** whose demethylation [18] led to 5-iodobenzene-1,3-diol (**5**). Compound **5** was used as an aglycone in the silver carbonate-mediated reaction [19] with **2** to afford the β-configurated glycoside **6** in 82 % yield. The anomeric configuration of **6** was deduced from the $^3J_{1\text{-H},2\text{-H}}$ coupling constant (8.2 Hz) which is typical for a *trans* 1-H/2-H (*i. e.* β-glycosidic) configuration in the pyranoside.

The starting material for the Heck coupling was obtained from 3-hydroxy-4-methoxy-benzaldehyde (**7**). Its Wittig olefination [20] using methyltriphenylphosphonium iodide in the presence of *t*BuOK gave styrene **8** in 84 % yield.

Heck-Mizoroki coupling reactions can be performed under a great variety [21, 22] of conditions. To avoid an extra protection/deprotection sequence, triethanolamine [23] was used both as a base, a ligand

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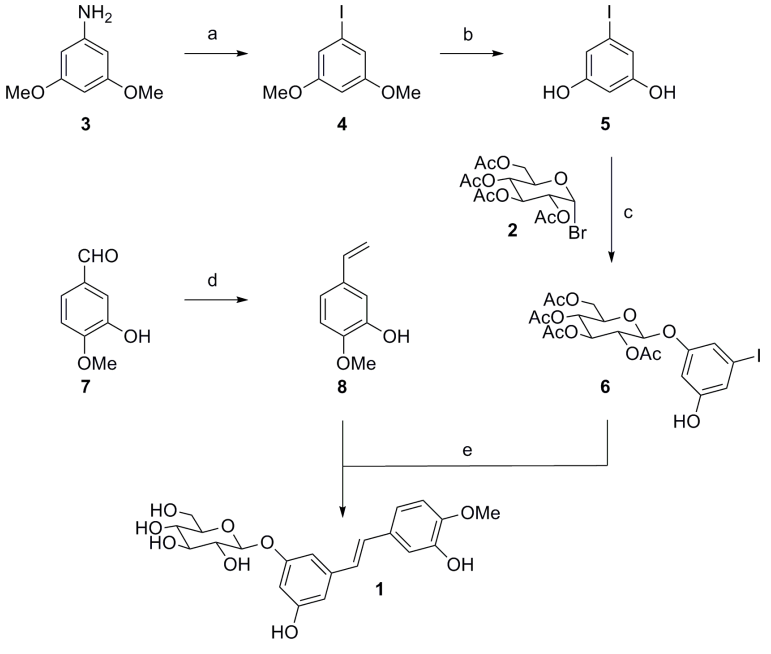
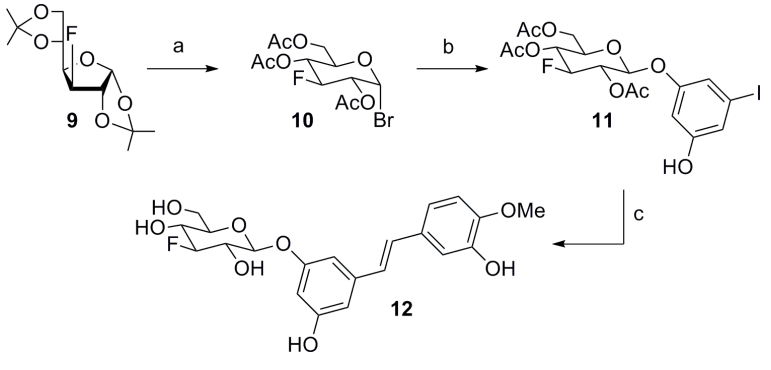


Scheme 1. a) $NaNO_2$/HCl, KI, 0→25 °C, 12 h, 76 %; b) BBr_3, CH_2Cl_2, −20→25 °C, 12 h, 72 %; c) Ag_2CO_3, CH_3CN, 25 °C, 8 h, 82 %; d) PPh_3CH_3I/*t*BuOK, THF, 25 °C, 12 h, 84 %; e) $Pd(OAc)_2$, $N(CH_2CH_2OH)_3$, 100 °C, 4 h, 82 %.



Scheme 2. a) H_2SO_4/H_2O, 25 °C, 24 h, then $Ac_2O/HClO_4$ in CH_2Cl_2, followed by HBr/HOAc, 25 °C, 12 h, 55 %; b) Ag_2CO_3, **5**, 25 °C, 8 h, 72 %; c) $Pd(OAc)_2$, **8**, $N(CH_2CH_2OH)_3$, 100 °C, 24 h, 74 %.

and a solvent. An additional advantage of these reaction conditions is the simultaneous cleavage of the acetyl groups from the sugar moiety during the coupling reaction. Therefore, **1** was obtained by the Heck-Mizoroki coupling in an 82 % isolated yield.

To perform binding studies, a route to the 3”-fluoro analog **12** (Scheme 2) seemed of interest and had to be established. A fluoro substituent is normally expected to be able to mimic the hydrogen bond-accepting properties of an OH group. The well accessible 3-deoxy-3-fluoro-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**9**) was transformed into the corresponding glucopyranosyl bromide **10** as described above. Compound **10** is characterized in its ^{19}F NMR spectrum by a multiplet at $\delta = -202.5$ ppm showing F, H coupling with $^2J_{F,3\text{-}H} = 54.5$ Hz, $^3J_{F,2\text{-}H} = 9.4$, and $^3J_{F,4\text{-}H} = 12.8$ Hz. Silver carbonate-mediated coupling of **10** with **5** gave a 72 % yield of the glycoside **11**. The ^1H NMR spectrum of **11** shows a $^3J_{1\text{-}H,2\text{-}H} = 7.3$ Hz being typical for a β-glycoside. Heck-Mizoroki coupling of **11** with the styrene **8** finally gave **12** in 74 % yield.

Experimental Section

General methods

Melting points are uncorrected (Leica hot stage microscope). Optical rotation data were obtained using a Perkin-Elmer 341 polarimeter (1 cm micro cell, 20 °C). NMR spectra were recorded using the Varian spectrometers Gemini 200, Gemini 2000 or Unity 500 (δ given in ppm, J in Hz, internal $SiMe_4$ or internal CCl_3F standards). IR spectra

(film or KBr pellet) were recorded on a Perkin-Elmer FT-IR spectrometer Spectrum 1000. Mass spectra were taken on an Intectra GmbH AMD 402 (electron impact, 70 eV) or a Thermo Electron Finnigan LCQ (electrospray, voltage 4.5 kV, sheath gas nitrogen) instrument. For elemental analysis a Foss-Heraeus Vario EL instrument was used. TLC was performed on silica gel (Merck 5554, detection by UV absorption or by treatment with a solution of 10 % sulfuric acid, ammonium molybdate and cerium(IV) sulfate, followed by gentle heating). The solvents were dried according to usual procedures.

*2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl bromide (**2**)*

Compound **2** was obtained from commercial penta-*O*-acetyl-α-D-glucopyranose and HBr/AcOH. Prior to use, **2** was re-crystallized from diisopropyl ether, and stored in the dark over KOH.

*1-Iodo-3,5-dimethoxybenzene (**4**)*

To a mixture of 3,5-dimethoxyaniline (**3**) (50.0 g, 326 mmol) and crushed ice (200 g) in aq. HCl (12 M, 200 mL, 2.4 mol), $NaNO_2$ (27 g, 390 mmol) was added in several small portions keeping the temperature at 0 °C. KI (550 g, 3.3 mol) was added in several portions. Stirring at 0 °C was continued for another 60 min, and then the mixture was allowed to warm to 25 °C over night. The mixture was extracted with diethyl ether (5 × 200 mL), washed with sodium sulfite, water and brine (50 mL each), followed by an evaporation of the solvent under diminished pressure. Purification of the crude product by chromatography (silica gel, hexane/ethyl acetate 9:1) furnished **4** (65.4 g, 76 %) as an off-white solid. M. p. 70 – 73 °C (lit. [24]: 74 – 75 °C). – IR (KBr): ν = 3442br, 3068s, 3006s, 2962s, 2929s, 2833s, 1710w, 1469s, 1450s, 1424s, 1294s, 1253m, 1197s, 1161s, 1032m cm^{-1}. – UV/Vis (MeOH): λ_{max} (log ε) = 230 nm (4.65). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.84 (d, 2 H, $^4J_{2\text{-H},6\text{-H}}$ = 2.3 Hz, 2-H, 6-H), 6.38 (s, 1 H, 4-H), 3.74 (s, 6 H, 2 × OCH_3). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.1 (C-3, C-5), 115.9 (C-2, C-6), 100.7 (C-4), 94.1 (C-1), 55.5 (2 × OCH_3). – MS (EI, 70 eV): *m/z* (%) = 264 (100), 236 (29), 221 (9), 122 (36). – $C_8H_9O_2I$ (264.06): calcd. C 36.39, H 3.44; found C 36.38, H 3.45.

*5-Iodobenzene-1,3-diol (**5**)*

Compound **4** (3.0 g, 11.3 mmol) was added in several portions to a solution of boron tribromide (3.0 mL, 31.6 mmol) in dry dichloromethane (50 mL) at −20 °C. The mixture was allowed to warm to 25 °C over night, diluted with water (25 mL) the pH being adusted to 10 (addition of conc. NaOH), and extracted with diethyl ether (2 × 50 mL). The pH of the aqueous phase was adjusted to 1 (addition of conc. HCl) and extracted with diethyl ether (2 × 50 mL). The combined organic phases were dried (Na_2SO_4), the solvent was removed, and **5** (1.93 g, 72 %) was obtained as a colorless solid. An analytical sample was obtained by flash chromatography. M. p. 92 – 95 °C (lit. [24]: 94 – 95 °C). – IR (KBr): ν = 3314br, 1609s, 1588s, 1481s, 1385m, 1347m, 1318m, 1294m, 1275m, 1216w, 1200w, 1152s cm^{-1}. – UV/Vis (MeOH): λ_{max} (log ε) = 230 nm (4.77). – ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.54 (s, 2 H, 2 × OH), 6.55 (d, 2 H, $^4J_{4\text{-H},6\text{-H}}$ = 2.1 Hz, 4-H, 6-H), 6.18 (s, 1 H, H-2). – ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 159.01 (C-1, C-3), 115.14 (C-4, C-6), 102.32 (C-2), 94.24 (C-5). – MS (EI, 70 eV): *m/z* (%) = 236 (100), 127 (7), 109 (30). – $C_6H_5O_2I$ (236.01): calcd. C 30.53, H 2.14; found C 30.51, H 2.15.

*(3-Hydroxy-5-iodophenyl) 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (**6**)*

To a solution of **5** (2.07 g; 8.8 mmol) and **2** (3.5 g, 8.5 mmol) in dry acetonitrile (20 mL), silver carbonate (2.4 g, 8.7 mmol) was added in several portions. The mixture was stirred at 25 °C for 8 h. The filtrate was evaporated and the crude product purified by chromatography (silica gel, hexane/ethyl acetate 2:1) to afford **6** (3.95 g, 82 %). M. p. 131 – 134 °C; $[\alpha]_D$ = −32.08° (*c* = 0.366, $CHCl_3$) (lit. [19]: −39.6° (*c* = 0.32, MeOH). – IR (KBr): ν = 3414br, 2952w, 1757m, 1611w, 1574w, 1486w, 1435w, 1375w, 1223m, 1174w, 1039m cm^{-1}. – UV/Vis (MeOH): λ_{max} (log ε) = 229 nm (3.51). – ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 6.91 (d, 2 H, $^4J_{2'\text{-H},6'\text{-H}}$ = 2.1 Hz, 2-H, 6-H), 6.45 (s, 1 H, 4-H), 5.91 (s, 1 H, phenolic OH), 5.28 – 5.19 (m, 2 H, 2’-H, 3’-H), 5.10 (m, 1 H, 4’-H), 5.00 (d, 1 H, $^3J_{1\text{-H},2\text{-H}}$ = 8.2 Hz, 1’-H), 4.21 – 4,18 (m, 2 H, 6’a-H, 6’b-H), 3.88 – 4.85 (m, 1 H, 5’-H), 2.14 – 2.10 (m, 12 H, 4 × CH_3). – ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 170.9, 170.3, 169.4 and 169.3 (each C=O of acetyl), 158.0 (C-5), 157.3 (C-3), 119.9 (C-2), 118.2 (C-6), 104.6 (C-4), 98.6 (C-1’), 93.6 (C-1), 72.6 (C-2’), 72.1 (C-5’), 71.0 (C-3’), 68.3 (C-4’), 62.0 (C-6’), 20.8 (2 × CH_3), 20.5 (2 × CH_3). – MS (EI, 70 eV): *m/z* (%) = 566 (4), 331 (33), 169 (100), 109 (46). – $C_{20}H_{23}O_{11}I$ (566.29): calcd. C 42.42, H 4.09; found C 42.40, H 4.11.

*2-Methoxy-5-vinyl-phenol (**8**)*

A solution of methyltriphenylphosphonium iodide (14.96 g, 37.0 mmol) and potassium *tert*-butoxide (4.48 g, 40.0 mmol) in dry THF (100 mL) was stirred for 30 min at 25 °C. 3-Hydroxy-4-methoxybenzaldehyde (**7**) (2.13 g, 14.0 mmol) was added in several portions, and stirring at 25 °C was continued for 12 h. The reaction mixture was diluted with a saturated aqueous solution of NH_4Cl (25 mL) and extracted with dichloromethane (4 × 25 mL).

The combined organic phases were dried (Na_2SO_4), the solvent was evaporated and the crude product purified by chromatography (silica gel, dichloromethane/hexane 3:1) to afford **8** (1.77 g, 84 %) as a slightly yellowish solid. M. p. 57 – 58 °C (lit. [25]: 56 – 57 °C). – IR (KBr): ν = 3317br, 3088m, 3005m, 2961m, 2933m, 2839m, 1612m, 1579s, 1512s, 1461m, 1440s, 1341s, 1271s, 1263s cm^{-1}. – UV/vis (MeOH): λ_{max} (log ε) = 233 nm (4.37). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.03 (d, 1 H, J = 1.9 Hz, 6-H), 6.84 (dd, 1 H, J = 8.2, 1.9 Hz, 4-H), 6.77 (d, 1 H, J = 8.2 Hz, 3-H), 6.61 (dd, 1 H, $^3J_{H,H\,(trans)}$ = 17.6 Hz, $^3J_{H,H\,(cis)}$ = 17.6 Hz, 7-H), 5.58 (d, 1 H, $^3J_{H,H(trans')}$ = 17.6 Hz, 8’a-H), 5.09 (d, 1 H, $^3J_{H,H(cis)}$ = 10.8 Hz, 8’b-H), 3.87 (s, 3 H, OCH_3). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.4 (C-2), 145.6 (C-1), 136.3 (C-7), 131.5 (C-5), 118.8 (C-4), 112.1 (C-8), 111.6 (C-6), 110.5 (C-3), 56.0 (OCH_3). – MS (EI, 70 eV): *m/z* (%) = 150 (57), 135 (100), 120 (53), 107 (32), 77 (37). – $C_9H_{10}O_2$ (150.17): calcd. C 71.98, H 6.71; found C 71.92, H 6.65.

*Rhaponticin (**1**)*

To a solution of **6** (1.66 g, 2.9 mmol) in triethanolamine (10 mL) containing palladium acetate (10 mg, 0.04 mmol), compound **8** (0.44 g, 2.9 mmol) was added, and the mixture was heated at 100 °C for 4 h. After cooling to 25 °C, ethanol (50 mL) was added, the mixture was filtered, and the solvents were removed from the filtrate under reduced pressure. The crude product was purified by chromatography (silica gel, dichloromethane/methanol 9:1) to afford **2** (1.03 g, 82 %) as a colorless solid. M. p. 235 – 238 °C (lit.: 230 °C [10], 236 – 238 °C [26]); $[\alpha]_D = -60.45°$ (c = 0.5, acetone), (lit. [27]: −59.5° (acetone)). – IR (KBr): ν = 3482br, 2900w, 2361w, 1758w, 1611w, 1584w, 1513w, 1460w, 1439w, 1317w, 1292w, 1260w, 1213w, 1175w, 1145w, 1132w, 1085w, 1059w, 1026w cm^{-1}. – UV/Vis (MeOH): λ_{max} (log ε) = 343 nm (4.45). – ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.00 (d, 1 H, $^4J_{2\text{-H},6\text{-H}}$ = 1.9 Hz, 2-H), 6.96 (d, 1 H, $^3J_{H,H}$ = 16.3 Hz, 1-H), 6.93 (dd, $^3J_{5\text{-H},6\text{-H}}$ = 8.5 Hz, $^4J_{2\text{-H},6\text{-H}}$ = 1.9 Hz, 6-H), 6.87 (d, 1 H, $^3J_{5\text{-H},6\text{-H}}$ = 8.5 Hz, 5-H), 6.82 (d, 1 H, $^3J_{H,H}$ = 16.3 Hz, 2-H), 6.71 (s, 1 H, 2’-H), 6.56 (s, 1 H, 6’-H), 6.33 (s, 1 H, 4’-H), 4.79 (d, 1 H, $^3J_{1\text{”-H},2\text{”-H}}$ = 7.6 Hz, 1”-H), 3.75 (s, 3 H, OCH_3), 3.59 (m, 2 H, 6”-CH_2), 3.33 (m, 1 H, 5”-H), 3.27 (m, 1 H, 3”-H), 3.21 (d, 1 H, $^3J_{1\text{”-H},2\text{”-H}}$ = 7.6 Hz, 2”-H), 3.15 (m, 1 H, 4”-H). – ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 159.0 (C-3’), 158.4 (C-5’), 147.8 (C-4), 146.7 (C-3), 139.2 (C-1’), 130.1 (C-1), 128.7 (CH=), 126.2 (CH=), 118.7 (C-6), 113.0 (C-2), 112.3 (C-5), 107.3 (C-6’), 105.0 (C-2’), 103.0 (C-4’), 100.7 (C-1”), 77.2 (C-5”), 76.8 (C-3”), 73.4 (C-2”), 69.9 (C-4”), 60.8 (C-6”), 55.7 (OCH_3). – MS (EI, 70 eV): *m/z* (%) = 420 (7), 278 (5), 258 (100), 225 (15), 197 (36), 169 (11), 150 (41), 135 (34). – $C_{21}H_{24}O_9$ .0.5 H_2O (429.42): calcd. C 58.74, H 5.87; found C 58.59, H 5.91.

*2,4,6-Tri-O-acetyl-3-deoxy-3-fluoro-α-D-glucopyranosyl bromide (**10**)*

A solution of 3-deoxy-3-fluoro-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**9**) (4.0 g, 15.2 mmol) in water (25 mL) containing conc. sulfuric acid (98 %, 2 mL) was stirred at 25 °C for 24 h. The reaction mixture was neutralized by careful addition of solid sodium hydrogencarbonate, and the solvents were removed under reduced pressure. The residue was suspended in methanol (50 mL), the mixture filtered and the filtrate evaporated. The residue was slowly added to a mixture of $HClO_4$ (70 %, 0.25 mL) in Ac_2O (5 mL) keeping the temperature < 30 °C. After completion of the reaction (as monitored by tlc), water (20 mL) was added, and the product was extracted with dichloromethane (4 × 25 mL). The organic layer was washed (aq. $NaHCO_3$, water, brine, 10 mL each) and dried (Na_2SO_4), and the solvents were evaporated. The residue was re-dissolved in dry dichloromethane (30 mL), and HBr in AcOH (6 mL, 30 %) was added. Stirring in the dark at 25 °C was continued for another 12 h. The reaction mixture was poured onto ice/water and extracted with dichloromethane (5 × 25 mL). The organic phase was washed ($NaHCO_3$, water, brine, 10 mL each), dried (Na_2SO_4) and evaporated to yield **10** (3.1 g, 55 %) as a highly viscous oil [28]. – $[\alpha]_D$ = + 174.4° (c = 0.3, $CHCl_3$). – IR (KBr): ν = 2948s, 2119m, 1747s, 1434s, 1371s, 1326m, 1215s, 1156s, 1112s, 1041s cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.57 (d, 1 H, $^3J_{1\text{-H},2\text{-H}}$ = 3.9 Hz, 1-H), 5.27 (ddd, 1 H, $^3J_{3\text{-H},4\text{-H}}$ = 8.9 Hz, $^3J_{4\text{-H},5\text{-H}}$ = 8.9 Hz, $^3J_{F,4\text{-H}}$ = 12.8 Hz, 4-H) 4.88 (ddd, 1 H, $^2J_{3\text{-H},F}$ = 54.5 Hz, $^3J_{3\text{-H},2\text{-H}}$ = 9.2 Hz, $^3J_{3\text{-H},4\text{-H}}$ = 8.9 Hz, 3-H), 4.87 (ddd, 1 H, $^3J_{2\text{-H},F}$ = 9.4 Hz $^3J_{2\text{-H},H\text{-}1}$ = 3.9 Hz, $^3J_{2\text{-H},3\text{-H}}$ = 8.9 Hz, H-2), 4.26 – 4.16 (m, 2 H, 6a,b-H), 4.19 (m, 1 H, H-5), 2.13, 2.11 and 2.07 (each s, 3 H, CH_3). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.3 (C=O), 169.6 (C=O), 169.0 (C=O), 89.4 (d, $^2J_{C,F}$ = 183.3 Hz, C-3), 86.2 (d, $^4J_{C,F}$ = 9.3 Hz, C-1), 72.1 (d, $^4J_{C,F}$ = 7.0 Hz, C-5), 70.9 (d, $^3J_{C,F}$ = 18.4 Hz, C-4), 71.9 (d, $^3J_{C,F}$ = 19.2 Hz, C-2), 67.2 (s, C-6) 20.6 (s, CH_3), 20.6 (s, CH_3), 20.5 (s, CH_3). – ^{19}F NMR (188 MHz, $CDCl_3$): δ = −202.5 (ddd, 1 F, $^2J_{F,3\text{-H}}$ = 54.5 Hz, $^3J_{F,2\text{-H}}$ = 9.4 Hz, $^3J_{F,4\text{-H}}$ = 12.8 Hz). – MS (EI, 70 eV): *m/z* (%) = 372 (0.05), 370 (0.05), 291 (3), 169 (24), 139 (3), 127 (9), 109 (18), 43 (100). – HRMS for $C_{12}H_{16}BrFO_4$ (371.15): calcd. 370.00634, found 370.00632.

*(3-Hydroxy-5-iodophenyl) 2,4,6-tri-O-acetyl-3-deoxy-3-fluoro-β-D-glucopyranoside (**11**)*

To a solution of **5** (2.1 g, 8.5 mmol) in acetonitrile (20 mL) at 25 °C, compound **10** (3.15 g, 8,5 mmol) was added, and the mixture was stirred for 30 min. Silver carbonate (2.4 g, 8.7 mmol) was added, and the mixture was stirred for another 8 h and filtered, and the solvents were removed from the filtrate. Chromatography (silica gel, hex-

ane/ethyl acetate 2:1) furnished **11** (3.22 g, 72 %) as a colorless solid. M. p. 139 – 142 °C; $[\alpha]_D = -32.0°$ (c = 0.3, $CHCl_3$). – IR (KBr): ν = 3422br, 2958w, 1748s, 1702m, 1607m, 1578m, 1484w, 1434m, 1375m, 1217s, 1170m, 1152m, 1040s cm^{-1}. – UV/Vis (MeOH): λ_{max} (log ε) = 228 nm (4.59). – ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 6.95 (dd, 1 H, $^4J_{2'\text{-H},6'\text{-H}}$ = 0.6 Hz, $^4J_{2'\text{-H},4'\text{-H}}$ = 1.4 Hz, 2’-H), 6.90 (dd, 1 H, $^4J_{6'\text{-H},H\text{-}2'}$ = 0.6 Hz, $^4J_{6'\text{-H},4'\text{-H}}$ = 1.4 Hz, 6’-H), 6.52 (dd, 1 H, $^4J_{4'\text{-H},2'\text{-H}}$ = 1.4 Hz, $^4J_{4'\text{-H},6'\text{-H}}$ = 1.4 Hz, 4’-H), 5.31 (d, 1 H, $^3J_{1\text{-H},2\text{-H}(trans)}$ = 7.3 Hz, 1-H), 5.26 (m, 1 H, 2-H), 5.20 (m, 1 H, 4-H), 4.88 (ddd, 1 H, $^2J_{3\text{-H,F}}$ = 52.5 Hz, $^3J_{3\text{-H},2\text{-H}}$ = 8.9 Hz, $^3J_{3\text{-H},4\text{-H}}$ = 8.9 Hz, 3-H), 4.19 (m, 2 H, 6a,b-H), 4.13 (m 1 H, 5-H), 2.09 – 2.04 (m, 9 H, CH_3). – ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 169.7 (C=O), 169.0 (C=O), 168.6 (C=O), 159.0 (C-5’), 158.5 (C-3’), 119.5 (C-2’), 116.9 (C-6’), 104.3 (C-4’), 97.8 (d, $^4J_{C,F}$ = 11.0 Hz, C-1), 93.3 (C-1’), 91.6 (d, $^2J_{C,F}$ = 187.9 Hz, C-3), 71.2 (C-5), 71.0 (d, $^3J_{C,F}$ = 8.1 Hz, C-2), 68.4 (d, $^3J_{C,F}$ = 18.5 Hz, C-4), 61.8 (C-6), 19.9, 19.8 and 19.7 (each CH_3). – ^{19}F NMR (188 MHz, [D$_6$]acetone): δ = −197.3 (ddd, $^2J_{F,3\text{-H}}$ = 51.6 Hz, $^3J_{F,2\text{-H}}$ = 12.9 Hz, $^3J_{F,4\text{-H}}$ = 12.5 Hz). – MS (ESI, MeOH): *m/z* (%) = 571.2 ([M+HCO$_2$]$^-$, 61), 561.2 ([M+Cl]$^-$, 6), 525 ([M–H]$^-$, 100). – $C_{18}H_{20}FIO_9$ (526.25): calcd. C 41.08, H 3.83; found C 40.87, H 3.91.

*3-Deoxy-3-fluoro-rhaponticin (3-hydroxy-5-[(E)-2-(3-hydroxy-4-methoxyphenyl)ethenyl]-phenyl 3-deoxy-3-fluoro-β-D-glucopyranoside) (**12**)*

To a solution of **8** (0.45 g, 3.0 mmol) in triethanolamine (15 mL), compound **11** (1.6 g, 3.0 mmol) and palladium acetate (10 mg, 0.04 mmol) were added, and the mixture was stirred under argon at 100 °C for 24 h. Work-up as described above followed by chromatography (silica gel, dichloromethane/MeOH 9:1) yielded **12** (0.95 g, 74 %) as a colorless solid. M. p. 163 – 165 °C; $[\alpha]_D = -50.2°$ (c = 0.3, $CHCl_3$). – IR (KBr): ν = 3423br, 2935w, 2370w, 1607w, 1514w, 1441w, 1384m, 1265w, 1166w, 1129w, 1076w, 1042w cm^{-1}. – UV/Vis (methanol): λ_{max} (log ε) = 219 nm (4.34), 326 nm (4.33). – ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 7.08 (d, 1 H, $^3J_{2\text{-H},6\text{-H}}$ = 2.1 Hz, 2-H), 7.04 (d, 1 H, $^3J_{H,H\ (trans)}$ = 16.4 Hz, =CH), 6.97 (dd, 1 H, $^3J_{6\text{-H},5\text{-H}}$ = 8.5 Hz, $^3J_{6\text{-H},2\text{-H}}$ = 2.1 Hz, 6-H), 6.91 (d, 1 H, $^3J_{5\text{-H},6\text{-H}}$ = 8.5 Hz, 5-H), 6.90 (d, 1 H, $^3J_{H,H\ (trans)}$ = 16.4 Hz, =CH), 6.80 (s, 1 H, 6’-H), 6.69 (s, 1 H, 2’-H), 6.47 (s, 1 H, 4’-H), 4.99 (*d*, 1 H, $^3J_{H,H\ (trans)}$ = 7.9 Hz, 1”-H), 4.42 (dt, $^3J_{H,H\ (trans)}$ = 8.7 Hz, $^2J_{H,F}$ = 52.3 Hz, 3”-H) 4.36 – 3.92 (m, 2 H, 6a,b-H), 3.84 (s, 3 H, OCH_3), 3.82 – 3.69 (m, 2 H, 4”-H, 5”-H), 3.58 – 3.55 (m, 1 H, 2”-H). – ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 160.0 (C-3’), 159.3 (C-5’), 147.6 (C-4), 147.5 (C-3), 140.6 (C-1’), 131.5 (C-1), 129.6 (=CH), 127.1 (=CH), 119.6 (C-6) 113.3 (CH-2), 112.4 (C-5), 108.4 (C-6’), 106.5 (C-2’), 103.9 (C-4’), 101.3(d, $^3J_{C,F}$ = 12.1 Hz, C-1”), 98.2 (d, $^1J_{C,F}$ =182.6 Hz, C-3”), 76.5 (d, $^3J_{C,F}$ = 8.1 Hz, C-5”), 73.0 (d, $^2J_{C,F}$ = 18.1 Hz, C-2”), 69.4 (d, $^2J_{C,F}$ = 16.5 Hz, C-4”), 62.1 (C-6”), 56.2 (OCH_3). – ^{19}F NMR (188 MHz, [D6]acetone): δ = −194.6 (ddd, $^2J_{F,3\text{-H}}$ = 53.0 Hz, $^3J_{F,2\text{-H}}$ = 14.2 Hz , $^3J_{F,4\text{-H}}$ = 14.2 Hz). – MS (EI, 70 eV): *m/z* (%) = 422 (7), 258 (100), 225 (12), 197 (35), 169 (10), 169 (11), 141 (7), 115 (8). – HRMS for $C_{21}H_{23}FO_8$ (422.40): calcd. 422.13769, found 422.13771.

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[1] S. Anagnostou, *Pharm. unserer Zeit* **2008**, *37*, 121 – 129.
[2] R. Engelshowe, *Pharm. unserer Zeit* **1995**, *14*, 40 – 49.
[3] M. Schmidt, R. Kimming, *Gynäkol. Geburtshilfl. Rundschau* **2006**, *46*, 166 – 173.
[4] P. Stute, L. Kiesel, *Gyn. Endokrinologie* **2004**, *2*, 91 – 93.
[5] I. Kubo, Y. Murai, *J. Nat. Prod.* **1991**, *54*, 1115 – 1118.
[6] M. Y. Yoo, K.-S. Oh, J. W. Lee, H. W. Seo, G. H. Yon, D. Y. Kwon, Y. S. Kim, S. Y. Ryn, B. H. Lee, *Phytother. Res.* **2007**, *21*, 186 – 189.
[7] H. Etoh, N. Yamashita, K. Sakata, H. Ina, K. Ina, *Agric. Biol. Chem.* **1990**, *54*, 2443 – 2444.
[8] A. M. Nyemba, M. Ngando, S. F. Kimbu, J. D. Conolly, *Phytochemistry* **1995**, *39*, 895 – 898.
[9] A. Tschirch, *Arch. Pharm.* **1899**, *237*, 632 – 637.
[10] A. Tschirch, *Arch. Pharm.* **1908**, *245*, 139 – 149.
[11] H. Hibasami, K. Takagi, T. Ishii, M. Tsujikawa, N. Imai, I. Honda, *Oncology Reports* **2007**, *18*, 347 – 351.
[12] Y. Kimura, M. Sumiyoshi, K. Baba, *Cancer Sci.* **2008**, *99*, 2083 – 2096.
[13] J. P. Steiner, A. Nath, W. Haughey, WO2008124131; *Chem. Abstr.* **2008**, 1248746.
[14] J. Milbrandt, B. Dasgupta, WO2008091710; *Chem. Abstr.* **2008**, 916619.
[15] G. Likhtenshtein, *Stilbenes. Applications in chemistry, life sciences and material science*, Wiley-VCH, Weinheim, **2010**, pp.1 – 41.
[16] L. Lamza, *J. Prakt. Chem.* **1964**, *25*, 294 – 300.
[17] H. Abe, K. Nishioka, S. Takeda, M. Arai, Y. Takeuchi, T. Harayama, *Tetrahedron Lett.* **2005**, *46*, 3197 – 3200.
[18] T. Cardolaccia, Y. Li, K. S. Schanze, *J. Am. Chem. Soc.* **2008**, *130*, 2525 – 2545.

[19] D. A. Learmonth, *Synth. Commun.* **2004**, *34*, 1565 – 1575.
[20] L. Castedo, J. E. Borges, C. F. Marcos, G. Yojo, *Synth. Commun.* **1995**, *25*, 1717 – 1728.
[21] R. F. Heck, *Org. React.* **1982**, *27*, 345 – 390.
[22] M. Oestreich (Ed.), *The Mizoroki-Heck reaction*, Wiley, Chichester, **2009**.
[23] H. J. Li, L. Wang, *Eur. J. Org. Chem.* **2006**, 5099 – 5102.
[24] B. Mariampillai, D. Alberico, V. Bidau, M. Lautens, *J. Am. Chem. Soc.* **2006**, *128*, 14436 – 14437.
[25] V. M. Rodionov, A. M. Fedorova, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1940**, 239 – 243.
[26] M. Henneber, *Biuletyn Instytutu Roslin Leczniczych* **1962**, *8*, 85 – 89; *Chem. Abstr.* **1963**, 428794.
[27] S. Kawamura, *Yakugaku Zasshi* **1938**, *58*, 405 – 413.
[28] D. Combaud, M. Thomas, S. Papot, J.-P. Gesson, *Lett. Drug Design Discovery* **2005**, *2*, 631 – 637.