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## Synthesis of inositol 2-phosphate–quercetin conjugates

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### Abstract

The antiproliferative flavonoid, quercetin, is limited in its pharmacological utility by its low water solubility. In this paper, we describe the synthesis of two quercetin analogues prepared by linking the hydroxyl group at the 3- or 5-position of the flavonoid to the 1-hydroxyl group of *myo*-inositol-2-phosphate via a succinate diester linkage. The resulting conjugates were found to have dramatically enhanced water solubility relative to quercetin; the 5-linked quercetin analogue **2** had a water solubility of > 300 mg/mL at 20 °C. Comparison of the *in vitro* cytotoxicity and antiproliferative activity of conjugate **2** with those of quercetin toward cultured human colon adenocarcinoma (SW480) and human glioblastoma (U87MG) cells indicated that this modification of quercetin does not significantly diminish its activity in these assays. © 1996 Elsevier Science Ltd.

*Keywords:* Inositol phosphates; Quercetin; Solubilized flavonoid conjugates

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### 1. Introduction

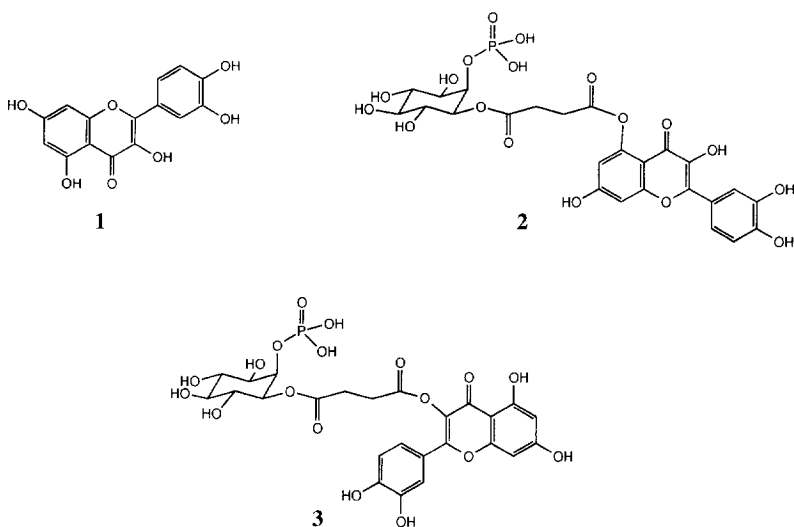
Flavonoids are a class of naturally occurring polyphenolic compounds which have been isolated from various vascular plants. They are a large constituent of the human

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<sup>1</sup> Deceased. The remaining authors dedicate this paper to the memory of Dr. Harry N. Antoniades.

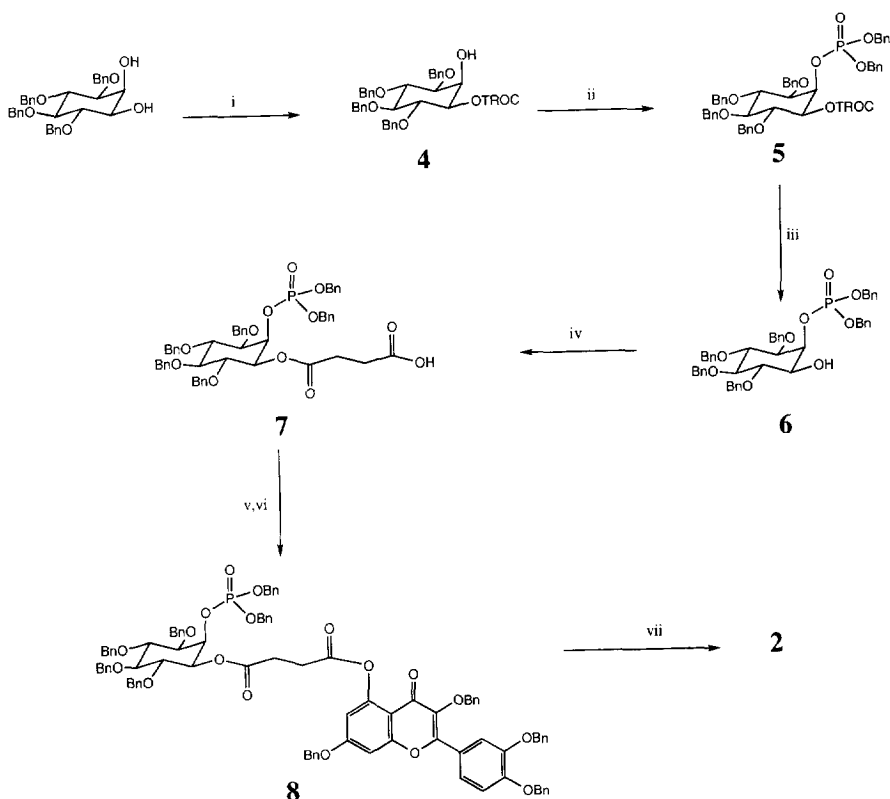
diet (~ 1 gram/day) [1] and have been shown to affect a wide variety of biological systems in mammals, exhibiting antioxidant, antiinflammatory, antiviral, antiproliferative, and anticarcinogenic effects [2]. One of the more abundant flavonoids, quercetin (3,3',4',5,7-pentahydroxyflavone, **1**), has been found to exert antiproliferative effects on human cells derived from breast [3], ovarian [4], leukemic [5], and colon [6] cancers. Quercetin has also been implicated in the regulation of heat shock protein synthesis [7] and human multidrug resistance [8]. Despite its *in vitro* biological activity, quercetin has seen little therapeutic use because it is practically insoluble in water.



While several naturally occurring glycosylated derivatives of quercetin are readily available (e.g. rutin and quercimeritrin), their water solubilities are poor (125 mg/mL and 'practically insoluble', respectively) [9] and they are known to suffer degradation by microbial glycosidases in the intestine [2]. Accordingly, we have undertaken a program to prepare flavonoid analogues with enhanced water solubility and bioavailability. We here report the synthesis of quercetin analogues **2** and **3**, in which an inositol 2-phosphate moiety has been attached to the 3- and 5-hydroxyl groups of the flavonoid via a succinate diester linkage. These conjugates were expected to possess high water solubility and may also benefit from enhanced bioavailability due to the active transport system known to exist for certain phosphorylated inositol glyicans [10].

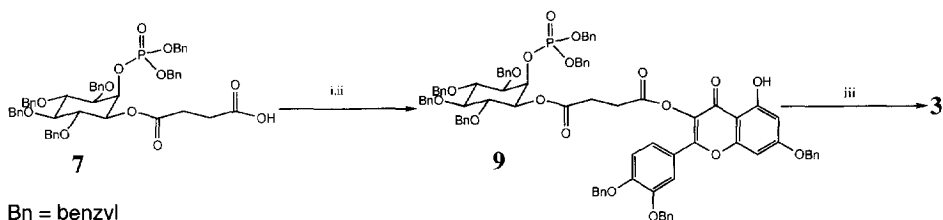
## 2. Results and discussion

The syntheses of conjugates **2** and **3** are depicted in Schemes 1 and 2. Racemic 1,4,5,6-tetra-*O*-benzyl-*myo*-inositol [11] was selectively acylated at the equatorial position with 1,1,1-trichloroethyl chloroformate to produce alcohol **4** in 79% yield. Phospho-



Scheme 1. (i) 1,1,1-Trichloroethyl chloroformate pyridine, 0 °C; (ii) dibenzyl *N,N*-diethylphosphoramidite, tetrazole, then MCPBA, -42 °C to r.t.; (iii) zinc dust, THF-HOAc-H<sub>2</sub>O (5:1:1); (iv) succinic anhydride, DMAP, 1,2-dichloroethane; (v) oxalyl chloride, benzene; (vi) 3,3',4',7-tetra-*O*-benzylquercetin, 1,2-dichloroethane; (vii) Pd/C (10%), ETOH-acetone (1:1), H<sub>2</sub>.

rylation under the conditions described by Fraser-Reid [12] resulted in a 83% yield of compound **5**. Removal of the trichloroethyl carbonate group was accomplished by treatment with zinc dust in a THF-H<sub>2</sub>O-HOAc mixture (5:1:1) to give alcohol **6** in 73% yield. Succinylation of **6** with succinic anhydride and DMAP in 1,2-dichloroethane



Scheme 2. (i) Oxalyl chloride, benzene; (ii) 3',4',7-tri-*O*-benzylquercetin, 1,2-dichloroethane; (iii) Pd/C (10%), ETOH-acetone (1:1), H<sub>2</sub>.

with an acidic workup gave **7** as an impure oil. Crude **7** was then converted into the corresponding acid chloride by treatment with oxalyl chloride. Without purification, the acid chloride was treated with 3,3',4',7-tetra-*O*-benzylquercetin [13] in the presence of DMAP to give the fluorescent compound **8** in 63% purified yield. Hydrogenolysis over 10% Pd–C in 1:1 ethanol–acetone gave the desired material, **2**, in quantitative yield.

A similar strategy was employed in the synthesis of compound **3**. The partially protected quercetin diol, 3',4',7-tri-*O*-benzylquercetin [13], was selectively acylated at the 3-hydroxyl group upon treatment with the acid chloride of succinate **7**, providing compound **9** in 71% yield. The regiochemistry of the product was assigned based on the presence of a singlet at 12.56 ppm in the <sup>1</sup>H NMR spectrum of **9**, which is known to be characteristic of the 5-OH of quercetin [14]. It is interesting to note that **9**, unlike **8**, is not fluorescent. Hydrogenolysis of **9** gave a quantitative yield of compound **3**.

The solubility of quercetin in water was found to be < 10 μg/mL at 20 °C. In marked contrast, synthetic analogues **2** and **3** were found to be highly soluble in water. Conjugate **2** exhibited a solubility exceeding 300 mg/mL at 20 °C, representing at least a 15,000 fold solubility enhancement over the unmodified flavonoid, on a molar basis.

The *in vitro* antiproliferative and cytotoxic activities of conjugate **2** and unmodified quercetin toward two cultured human malignant cell-lines were compared at both 28 μM and 150 μM. Selected for assay were a colon adenocarcinoma cell line (SW480) and a glioblastoma cell line (U87MG). The two compounds were found to have identical antiproliferative and cytotoxic activities within experimental error. These results demonstrate that the presence of the succinyl–inositol–phosphate moiety does not appreciably diminish quercetin's activities in these *in vitro* assays.

An *in vivo* evaluation of the antitumor efficacy of these compounds in nude mice is underway. The results of this study will shed light on the potential clinical value of enhancing the solubility of quercetin by this modification.<sup>2</sup>

### 3. Experimental

*General methods.*—All nonaqueous reactions were carried out under an argon or nitrogen atmosphere. Organic extracts were dried with anhydrous MgSO<sub>4</sub>. Solvents and reagents obtained from commercial sources were used without further purification with the following exceptions: dichloromethane and 1,2-dichloroethane were distilled from P<sub>2</sub>O<sub>5</sub>. *N,N*-Dimethylformamide (DMF), acetonitrile, and pyridine were distilled at reduced pressure from calcium hydride. Tetrahydrofuran (THF), diethyl ether, and benzene were distilled from sodium benzophenone ketyl. Reactions were monitored by TLC on Baker glass-backed silica gel plates (0.25-mm thickness). The chromatograms were visualized either under UV light (254-nm fluorescent indicator) or by dipping in an ethanolic solution of Hanes–Isherwood stain (ammonium molybdate–HCl–perchloric acid–acetone) [15]. Preparative separations were performed by flash chromatography on Baker silica gel (40 mm). The <sup>1</sup>H and <sup>31</sup>P NMR spectra were recorded with a Bruker

<sup>2</sup> Details of both *in vitro* and *in vivo* comparison of quercetin with conjugate **2** will be reported elsewhere.

300 MHz spectrometer. Tetramethylsilane and  $\text{H}_3\text{PO}_4$  were used as references, respectively.

*1,4,5,6-Tetra-O-benzyl-myo-inositol 3-(2,2,2-trichloroethyl carbonate)* (**4**).—To 773 mg of *1,4,5,6-tetra-O-benzyl-myo-inositol* [11] (1.43 mmol, azeotropically dried with toluene) in 4.0 mL of pyridine was added 197  $\mu\text{L}$  (1.43 mmol) 1,1,1-trichloroethyl chloroformate at 0 °C. The reaction was stirred at 0 °C for 1 h. The reaction mixture was diluted with 2 mL of dichloromethane, and the organic phase was washed with water (3  $\times$  2 mL), dried, and evaporated. Heptane was evaporated from the crude product until pyridine was no longer detected by smell, and the product was chromatographed on silica gel with 3:1 hexane–ether ( $R_f$  0.15) providing **4** as an oil (809 mg, 79% yield);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.53 (s, 1 H, OH), 3.51–3.57 (m, 2 H), 3.97 ( $\psi\text{t}$ , 1 H,  $J$  9.7 Hz), 4.14 ( $\psi\text{t}$ ,  $J$  9.7 Hz, 1 H), 4.34–4.39 (m, 1 H, H-2), 4.61–4.79 (m, 6 H), 4.84–4.91 (m, 5 H), 7.24–7.38 (m). Anal. Calcd for  $\text{C}_{37}\text{H}_{37}\text{Cl}_3\text{O}_8$ : C, 62.06; H, 5.21; Cl, 14.85. Found: C, 62.33; H, 5.23; Cl, 14.94.

*1,4,5,6-Tetra-O-benzyl-2-O-(dibenzoyloxyphosphoryl)-myo-inositol 3-(2,2,2-trichloroethyl carbonate)* (**5**).—To 1.54 g of **4** (2.15 mmol, azeotropically dried with toluene) and 455 mg of 1*H*-tetrazole (6.49 mmol) was added 9.0 mL MeCN and 2.16 mL of dibenzyl *N,N*-diethylphosphoramidite (7.09 mmol). The reaction was stirred at room temperature for 20 min. The mixture was then cooled to –42 °C (MeCN– $\text{CO}_2$ ) and 7.80 mL of 1 M 85% *m*-chloroperoxybenzoic acid (7.80 mmol) in  $\text{CH}_2\text{Cl}_2$  was added. The cooling bath was immediately removed and the mixture allowed to warm to room temperature. After 10 min, 5 mL of 0.1 M  $\text{NH}_4\text{–HCO}_3$  buffer (pH 7.87) and 5 mL of 10%  $\text{Na}_2\text{S}_2\text{O}_4$  were added. The crude mixture was extracted with  $\text{CH}_2\text{Cl}_2$ . The organic layer was washed with water (1  $\times$  5 mL), 1 M  $\text{NaHCO}_3$  (5  $\times$  5 mL), dried, and evaporated. The crude products were chromatographed on silica gel with 19:1 benzene–EtOAc ( $R_f$  0.33) providing 1.80 g of **5** as an oil (83% yield);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  –1.41;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.54–3.63 (m, 2 H), 3.90 ( $\psi\text{t}$ ,  $J$  9.5 Hz, 1 H), 3.97 ( $\psi\text{t}$ ,  $J$  9.5 Hz, 1 H), 4.59 (d,  $J$  10.9 Hz, 1 H, 1/2  $\text{CH}_2\text{Ph}$ ), 4.63 (d,  $J$  9.8 Hz, 1 H, 1/2  $\text{CH}_2\text{Ph}$ ), 4.67 (d,  $J$  10.9 Hz, 1 H, 1/2  $\text{CH}_2\text{Ph}$ ), 4.72–4.92 (m, 8 H), 4.96–5.00 (m, 2 H,  $\text{CH}_2\text{Ph}$ ), 5.12–5.16 (m, 2 H,  $\text{CH}_2\text{Ph}$ ), 5.37 (dt,  $J$  2.3, 8.6 Hz, 1 H, H-2), 7.12–7.43 (m). Anal. Calcd for  $\text{C}_{51}\text{H}_{50}\text{Cl}_3\text{O}_{11}\text{P}$ : C, 62.74; H, 5.16; Cl, 10.89; P, 3.17. Found: C, 62.61; H, 5.22; Cl, 11.07; P, 3.05.

*1,4,5,6-Tetra-O-benzyl-2-O-(dibenzoyloxyphosphoryl)-myo-inositol* (**6**).—To 664 mg of **5** (0.669 mmol) was added 10 mL of 5:1:1 THF–HOAc– $\text{H}_2\text{O}$  and 1.108 g of zinc dust. The mixture was stirred at room temperature for 1 h. An additional 1.108 g of zinc dust was added and the mixture was stirred for 1 h at room temperature. The mixture was filtered through Celite, and diluted with  $\text{CH}_2\text{Cl}_2$ . The organic layer was washed with water (1  $\times$  5 mL), dried, and evaporated. The crude products were chromatographed on silica gel with 8:1 benzene–EtOAc ( $R_f$  = 0.09) providing **6** as an oil (400 mg, 73% yield).  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  –0.95;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.86 (d,  $J$  5.0 Hz, 1 H, OH), 3.47–3.53 (m, 2 H), 3.54–3.59 (m, 1 H, H-3), 3.73 ( $\psi\text{t}$ ,  $J$  9.4 Hz, 1 H), 3.86 ( $\psi\text{t}$ ,  $J$  9.4 Hz, 1 H), 4.55 (d,  $J$  11.1 Hz, 1 H, 1/2  $\text{CH}_2\text{Ph}$ ), 4.71 (d,  $J$  11.2 Hz, 1 H, 1/2  $\text{CH}_2\text{Ph}$ ), 4.73 (d,  $J$  10.7 Hz, 1 H, 1/2  $\text{CH}_2\text{Ph}$ ), 4.80–5.12 (m, 10 H), 7.16–7.39 (m). Anal. Calcd for  $\text{C}_{48}\text{H}_{49}\text{O}_{11}\text{P}$ : C, 71.99; H, 6.17; P, 3.87. Found: C, 71.60; H, 6.03; P, 3.70.

*1,4,5,6-Tetra-O-benzyl-2-O-(dibenzoyloxyphosphoryl)-myo-inositol 3-(hydrogen succinate)* (**7**).—To 200 mg of **6** (0.240 mmol, azeotropically dried with toluene) was added 123 mg of succinic anhydride (1.23 mmol), 150 mg of 4-dimethylaminopyridine (1.23 mmol), and 5 mL 1,2-dichloroethane. The mixture was stirred for 2 h at room temperature, cooled to 0 °C and 12 mL of 0.5 M NaHSO<sub>4</sub>–Na<sub>2</sub>SO<sub>4</sub> buffer (pH = 1.0) was added. The crude mixture was stirred for 5 min at 0 °C and then extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was washed with water (3 × 5 mL), dried, and evaporated. The crude products were chromatographed on silica gel with 5:2 benzene–EtOAc (*R<sub>f</sub>* = 0.05) providing 180 mg of **7** as an oil (82% crude yield); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ –2.13; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.37–2.64 (m, succinate and impurity), 3.53–3.61 (m, 2 H), 3.88 (*ψ*t, *J* 9.6 Hz, 1 H), 3.93 (*ψ*t, *J* 9.6 Hz, 1 H), 4.58 (d, *J* 10.9 Hz, 1 H, 1/2 CH<sub>2</sub>Ph), 4.63 (d, *J* 11.3 Hz, 1 H, 1/2 CH<sub>2</sub>Ph), 4.72–4.96 (m, 9 H), 5.05 (m, 2 H, CH<sub>2</sub>Ph), 5.20 (d*ψ*t, *J* 2.1, 8.5 Hz, 1 H), 7.08–7.15 (m, 2 H), 7.18–7.38 (m).

*3,3',4',7-Tetra-O-benzylquercetin 5-[1,4,5,6-tetra-O-benzyl-2-O-(dibenzoyloxyphosphoryl)-myo-inositol 3-succinate]* (**8**).—To 88.2 mg of crude **7** (0.0963 mmol) was added 6.0 mL of benzene and 200 μL (2.3 mmol) of oxalyl chloride. The mixture was stirred for 2.5 h at room temperature. The solvent was removed in vacuo under anhydrous conditions and then the residue was dissolved in 2 mL of 1,2-dichloroethane. This solution was added to 128 mg (0.193 mmol) of 3,3',4',7-tetra-*O*-benzylquercetin [**13**] (azeotropically dried with toluene) and 23.6 mg (0.193 mmol) of 4-dimethylaminopyridine in 1.5 mL 1,2-dichloroethane. The mixture was stirred for 5 min and then quenched with 2 mL of pH 7.0 phosphate buffer (0.1 M) and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was washed with water (3 × 1.5 mL), dried, and evaporated. The crude products were chromatographed on silica gel with 8:1 benzene–EtOAc (*R<sub>f</sub>* 0.22) providing 94.5 mg of **8** as an oil (62% yield); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ –1.51; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.73–2.78 (m, 2 H, succinate), 3.03–3.17 (m, 2 H, succinate), 3.52–3.61 (m, 2 H), 3.91 (*ψ*t, *J* 9.5 Hz, 1 H), 3.97 (*ψ*t, *J* 9.5 Hz, 1 H), 4.55 (d, *J* 10.9 Hz, 1 H, 1/2 CH<sub>2</sub>Ph), 4.68 (d, *J* 11.2 Hz, 1 H, 1/2 CH<sub>2</sub>Ph), 4.71 (d, *J* 10.9 Hz, 1 H, 1/2 CH<sub>2</sub>Ph), 4.75 (d, *J* 10.7 Hz, 1 H, 1/2 CH<sub>2</sub>Ph), 4.81–4.86 (m, 4 H), 4.87–4.97 (m, 7 H), 5.02–5.07 (m, 2 H, CH<sub>2</sub>Ph), 5.10 (s, 2 H, CH<sub>2</sub>Ph), 5.20–5.27 (m, 3 H), 6.71 (d, *J* 2.4 Hz, 1 H, H-6 or H-8 quercetin), 6.81 (d, *J* 2.4 Hz, 1 H, H-6 or H-8 quercetin), 6.92 (d, *J* 8.7 Hz, 1 H, H-5' quercetin), 7.13–7.49 (m), 7.65 (d, *J* 2.1 Hz, 1 H, H-2' quercetin).

*Quercetin-5-(2-O-phosphono-myoinositol 1-succinate)* (**1**).—To 47.3 mg of **8** (0.030 mmol) was added 2 mL of 1:1 ethanol–acetone and 9.5 mg of 10% Pd/C. The mixture was placed into a Parr apparatus under 36 psi of hydrogen for 11 h. The reaction mixture was filtered through Celite and the residue was washed consecutively with 3 mL of acetone, 1:1 acetone–water, and water. The filtrate and combined washes were evaporated providing **1** (quantitative yield). UV(H<sub>2</sub>O) λ<sub>max</sub> 357, 264, 205 nm<sup>3</sup>; <sup>31</sup>P NMR (D<sub>2</sub>O) δ 4.14; <sup>1</sup>H NMR (D<sub>2</sub>O) δ 2.68–2.81 (m, 2 H, CH<sub>2</sub>), 2.84–2.98 (m, 2 H, CH<sub>2</sub>),

<sup>3</sup> For comparison: UV (CH<sub>2</sub>Cl<sub>2</sub>) for 3,3',4',7-tetra-*O*-benzylquercetin: λ<sub>max</sub> 352, 267, 257, and 227 nm; UV (ethanol) for quercetin dihydrate: λ<sub>max</sub> 377, 256, and 205 nm.

3.10–3.21 (m), 3.39–3.58 (m, 3 H), 3.67–3.79 (m, 1 H), 4.48–4.70 (m), 6.11 ( $\psi$ s, 1 H, H-6 or H-8 quercetin), 6.30 ( $\psi$ s, 1 H, H-6 or H-8 quercetin), 6.89, (d, 1 H, H-5' quercetin), 7.17–7.31 (m, 2 H, H-2' and H-6' quercetin)<sup>4</sup>; FABMS exact mass calcd for C<sub>25</sub>H<sub>25</sub>O<sub>18</sub>P (M-H)<sup>-</sup> 643.0700, found 643.0713.

**3',4',7-Tri-O-benzylquercetin 3-[1,4,5,6-tetra-O-benzyl-2-O-(dibenzoyloxyphosphoryl)-myo-inositol 3-succinate] (9).**—To 25.7 mg of crude **7** (28.5  $\mu$ mol) was added 1 mL of benzene and 60  $\mu$ L (684  $\mu$ mol) of oxalyl chloride. The mixture was stirred at room temperature for 2 h. The solvent was removed in vacuo under anhydrous conditions, then the residue was dissolved in 400  $\mu$ L 1,2-dichloroethane. To the reaction mixture was added 26 mg of 3,3',4'-tri-O-benzylquercetin [13] (43  $\mu$ mol, azeotropically dried with toluene) and 5.3 mg of 4-dimethylaminopyridine (43  $\mu$ mol) in 300  $\mu$ L 1,2-dichloroethane. The mixture was stirred for 15 min, then diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed with water (3  $\times$  1.5 mL), dried, and evaporated. The crude products were chromatographed on silica gel with 8:1 benzene–EtOAc (*R<sub>f</sub>* 0.52) providing 30.0 mg of **9** as an oil (71% yield); <sup>31</sup>P NMR (CDCl<sub>3</sub>)  $\delta$  -1.56; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  2.38–2.84 (m, 4 H, succinate), 3.44 ( $\psi$ t, *J* 9.4 Hz, 1 H), 3.47 (d $\psi$ t, *J* 2.3, 9.8 Hz, 1 H, H-1 inositol), 3.79 ( $\psi$ t, *J* 9.4 Hz, 1 H), 3.84 ( $\psi$ t, *J* 9.8 Hz, 1 H), 4.44 (d, *J* 11.0 Hz, 1 H, 1/2 CH<sub>2</sub>Ph), 4.53 (d, *J* 11.3 Hz, 1 H, 1/2 CH<sub>2</sub>Ph), 4.62–4.80 (m, 7 H, 3 CH<sub>2</sub>Ph and H-2 or H-3 inositol), 4.83 (d, *J* 6.5 Hz, 1 H, 1/2 CH<sub>2</sub>Ph), 4.84 (d, *J* 7.0 Hz, 1 H, 1/2 CH<sub>2</sub>Ph), 4.89, 4.92 (AB quartet, 2 H, CH<sub>2</sub>Ph), 4.97, 4.99, 5.02 (3  $\psi$ s, 6 H, 3 CH<sub>2</sub>Ph), 5.10 (dt, *J* 2.3, 8.7 Hz, 1 H, H-2 or H-3 inositol), 6.32 (d, *J* 2.2 Hz, 1 H, H-6 or H-8 quercetin), 6.39 (d, *J* 2.2 Hz, 1 H, H-6 or H-8 quercetin), 6.86 (d, *J* 8.8 Hz, 1 H, H-5' quercetin), 6.99–7.30 (m), 7.65 (d, *J* 2.2 Hz, 1 H, H-2' quercetin), 7.78 (dd, *J* 2.2, 8.8 Hz, 1 H, H-6' quercetin), 12.56 (broad s, 1 H, 5-OH quercetin).

**Quercetin 3-(2-O-phosphono-myoinositol 1-succinate (3)).**—To 30 mg of **9** (20.1  $\mu$ mol) was added 2 mL of 1:1 ethanol–acetone and 6.0 mg of 10% Pd/C. The mixture was placed into a Parr apparatus under 36 psi of hydrogen for 15 h. The reaction mixture was filtered through Celite and the filtrate was washed consecutively with 3 mL of acetone, 1:1 acetone–water, and water. The filtrate was evaporated giving compound **3** in quantitative yield; <sup>31</sup>P NMR (D<sub>2</sub>O)  $\delta$  3.81; <sup>1</sup>H NMR (D<sub>2</sub>O)  $\delta$  2.51–2.93 (vbs), 3.21–3.36 (vbs), 3.52–3.63 (vbs), 3.71–3.87 (vbs), 4.48–4.54 (vbs), 5.47–5.71 (vbs), 6.36–6.58 (vbs), 6.83–7.22 (vbs)<sup>4</sup>; FABMS exact mass, calcd for C<sub>25</sub>H<sub>25</sub>O<sub>18</sub>P (M-H)<sup>-</sup> 643.0700, found 643.0703.

## Acknowledgements

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<sup>4</sup> For comparison: <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>) for quercetin:  $\delta$  6.25 (*d*, *J* 2.1 Hz, 1 H, H-6 or H-8), 6.51 (*d*, *J* 2.1 Hz, 1 H, H-6 or H-8), 6.98 (*d*, *J* 8.5 Hz, 1 H, H-5'), 7.69 (dd, *J* 2.2, 8.5 Hz, 1 H, H-6'), 7.82 (*d*, *J* 2.2, 1 H, H-2'), 8.00 (s, 1 H, OH), 8.30 (s, 1 H, OH), 8.52, (s, 1 H, OH), 9.66 (s, 1 H, OH), 12.16 (s, 1 H, 5-OH).

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