Synthesis and Biological Evaluation of Decursin, Prantschimgin and Their Derivatives

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The synthesis of coumarin-based natural products and their derivatives is described. *In vitro* MDR reversal activities of the synthesized compounds were evaluated in P-glycoprotein over-expressing human sarcoma cell line MES-SA/DX5. Some of the coumarin derivatives were found to show potent MDR reversal activity. In particular, pyridyl derivative (**15e**) exhibited more potency than verapamil.

Key Words: Coumarins, Decursin, Prantschimgin, Multidrug resistance, P-glycoprotein

Introduction

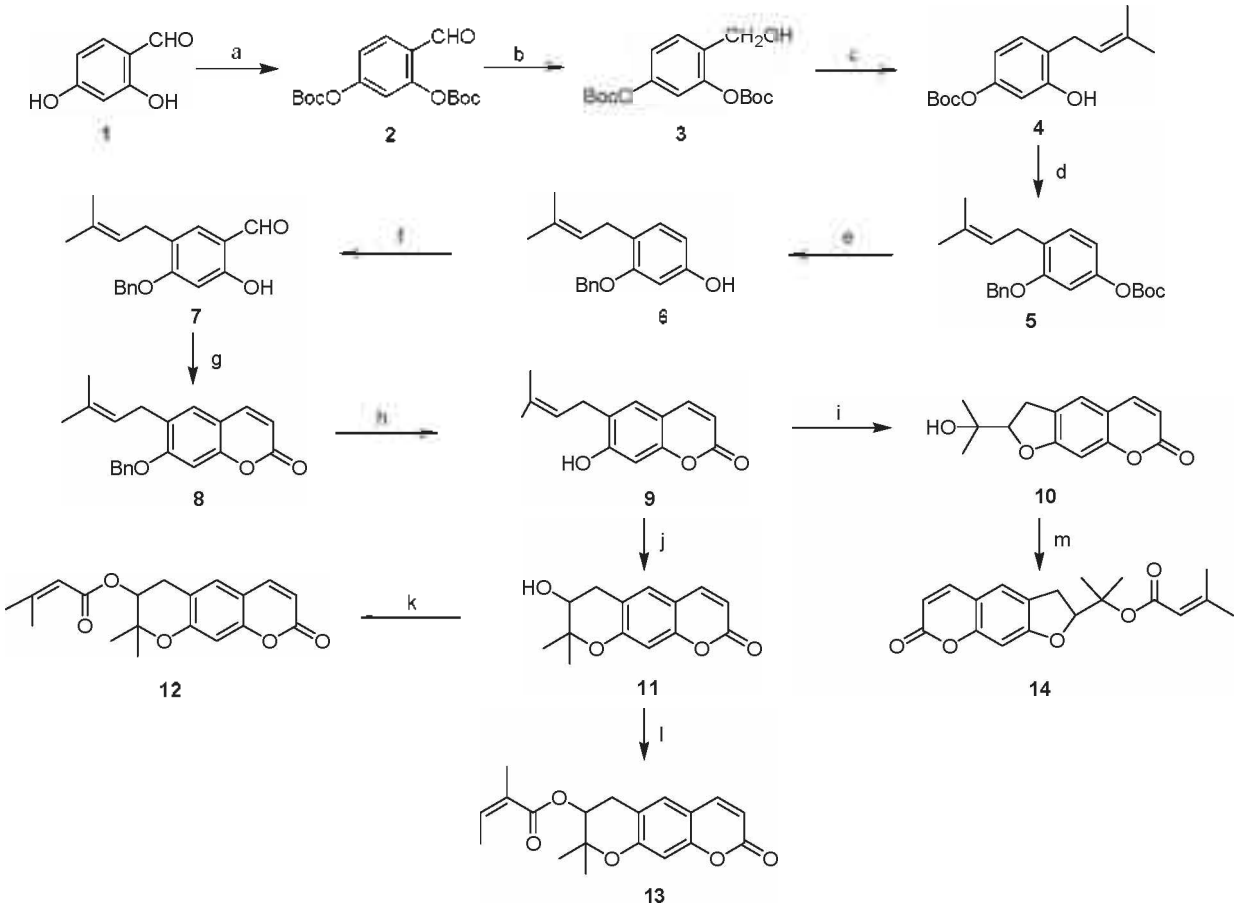
Natural products bearing coumarin moiety have shown a variety of biological activities.[1] Especially, coumarins isolated from *Angelica gigas* exhibit neuroprotective,[2] antitumor,[3] antinociceptive,[4] antibacterial,[5] platelet antiaggregatory[6] and protein kinase C (PKC) activation activities.[7] Coumarins of *A. gigas* contain a series of dihydropyranocoumarins, including (+)-decursin, (+)-decursinol angelate, (−)-prantschimgin, (+)-decursinol, and (−)-marmesin. Recently decursin and decursinol angelate have attracted considerable attention due to their remarkable biological activities,[8] and their asymmetric syntheses have been reported.[9] In view of such diverse biological activities, it is of interest to construct a coumarin library in order to generate biologically interesting lead compounds. Accordingly, it has driven us to synthesize the coumarin derivatives and investigate their biological activities.

As part of our program for development of novel multidrug resistance (MDR) modulators, we have screened a library of natural products including coumarins and synthetic molecules. Multidrug resistance (MDR) that disables most potent anticancer drugs is one of major problems in chemotherapy.[10] Intensive biochemical and clinical studies have demonstrated that overexpression of P-glycoprotein (Pgp), an ATP-binding cassette transporter, is largely responsible for MDR and clinically more significant than other mechanisms. Although a number of compounds with the effect of inhibiting Pgp have been developed, no useful drug is available so far. There is still high unmet clinical need for novel Pgp inhibitors. For the excavation of Pgp-selective MDR modulators, we have established image based high-throughput screening system and identified a series of coumarins that reverse Pgp-mediated MDR. We herein report an efficient synthesis of coumarins and their MDR reversal activity.

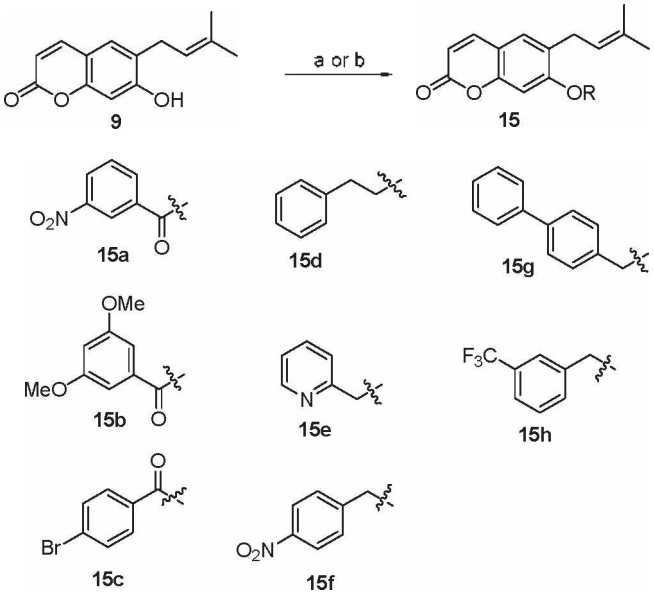
Results and Discussion

Chemistry. The syntheses of the target compounds were accomplished as indicated in Scheme 1 and 2. The intermediate, *ortho*-prenylated phenol **4** was readily prepared as described in the literature.[11] starting from 2,4-dihydroxybenzaldehyde **1**. Boc protection of **1**, followed by $NaBH_4$ reduction, gave alcohol **3** in 63% yield (2 steps). Addition of excess of Grignard reagent to the alcohol **3** afforded *ortho*-prenylated phenol **4**. Benzyl protection of this phenol **4** and subsequent removal of the Boc group under acidic condition afforded benzyloxy prenylated phenol **6**. Then treatment of triethylorthoformate in the presence of $AlCl_3$ introduced formyl group in 35% yield. Heating the aldehyde **7** with (carbethoxymethylene)-triphenylphosphorane in diethylaniline gave prenylated coumarin **8** in 84% yield. Debenzylation of **8** with Raney nickel furnished demethylsuberosin (**9**), which was converted into racemic marmesin (**10**) and decursinol (**11**) under basic and acidic conditions, respectively. Decursinol angelate (**12**) and decursin (**13**) were obtained by coupling of decursinol with angelic acid and senecioyl chloride, respectively. DCC mediated coupling of marmesin (**10**) with angelic acid provided prantschimgin (**14**). Naturally occurring coumarins, marmesin (**10**), decursinol (**11**), decursinol angelate (**12**), decursin (**13**) and prantschimgin (**14**) were efficiently obtained from intermediate **9**. We next turned our attention to synthesize new coumarin derivatives. Alkylation or acylation of intermediate **9** conveniently generated coumarin derivatives, **15a-15h** (Scheme 2). It should be noted that our synthetic method could be useful for bestowing diversity on coumarin scaffold.

Biological evaluation. The reversal activity of the synthesized coumarins was evaluated in Pgp over-expressing human sarcoma cell line MES-SA/DX5. Enhancing effects of compounds on the cytotoxicity of Taxol (paclitaxel) against MES-SA/DX5 were determined in the presence of 5 μM of each compound. Taxol exhibited IC_{50} value of about 6 μM against the MDR cancer cells, whereas showing one or two digit nanomolar inhibition against most sensitive cancer cells. Only prantschimgin among natural coumarins showed weak MDR reversal activity. Co-treatment with 5 μM of prantschimglin caused a 5.8-fold increase in cytotoxicity of Taxol for MDR cancer cells. Reversal activity of coumarin derivatives was evaluated as well. Ether derivatives of demethylsuberosin (**9**), **15d-15f** exhibited MDR reversal activity, but esters **15a-15c** did not show any significant activity.



Scheme 1. Synthesis of Marmesin, Decursinol and their analogues. Reaction Conditions: (a) $(Boc)_2O$, K_2CO_3, ether, rt, 90%; (b) $NaBH_4$, THF, conc HCl, AcOH, 0 °C, 15 min, 70% (c) 2-methyl-1-propenyl magnesium bromide, THF, 0 °C to rt, 10 h, 71% (d) BnBr, K_2CO_3, DMF, rt, 12 h, 81% (e) 1M HCl in dioxane, MeOH, rt, 91% (f) $CH(OEt)_3$, $AlCl_3$, benzene, rt, 30 min, 48% (g) (carbethoxymethylene)triphenylphosphorane, *N,N*-diethyl aniline, 190 °C, 5 h, 89% (h) Raney Ni, EtOH, rt, 3 h, 90% (i) *m*-chloroperbenzoic acid, $NaHCO_3$, $CHCl_3$, $NaHSO_3$, NaOH, 0 °C to rt, 3 h, 80% (j) *m*-chloroperbenzoic acid, *p*-toluenesulfonic acid, $CHCl_3$, rt, 12 h, 72% (k) DCC, angelic acid, DMAP, rt, 26 h, 38% (l) LiHMDS, DMAP, senecioyl chloride, -40 °C, 18 h, 36% (m) DCC, angelic acid, 30 °C, 24 h, 48%



Scheme 2. Synthesis of the derivatives of Intermediate **9**. Reaction Conditions: (a) DCC, DMAP, RCO_2H, CH_2Cl_2, rt (62% for **15a**, 53% for **15b**, 74% for **15c**); (b) K_2CO_3, RBr, DMF, rt (83% for **15d**, 79% for **15e**, 82% for **15f**, 78% for **15g**, 92% for **15h**)

Introduction of 4-nitrobenzyl group (**15f**) led to a 10-fold increase of cytotoxicity of Taxol. Of interest, pyridyl derivative **15e** showed remarkable MDR reversal activity, which is 1.4-fold better than verapamil, a well-known Pgp inhibitor.[12]

In conclusion, we have established synthetic method for biologically interesting coumarins of *A. gigas*. Intermediate in the synthetic pathway was further utilized to synthesize new coumarin derivatives. Some of the synthesized coumarins showed MDR reversal activity. In particular, compound **15e** exhibited activity better than verapamil and can be a candidate for further investigation.

Experimental Section

All of the commercial chemicals and solvents are of reagent grade and were used without further purification. All reactions were carried out under an atmosphere of dried argon in flame-dried glassware. Proton nuclear magnetic resonance (^{1}H NMR) spectra were determined on a Varian (300 MHz) spectrometer. Mass spectra were recorded on a Finnigan ESI mass spectrometer was obtained on a Mariner instrument (Perseptive Biosystem). Products from all reactions were purified to a minimum purity of 96% as determined by HPLC.

Table 1. MDR reverting activity of the coumarins[a]

Compound[b]	IC_{50} of Taxol (μM)[c]	Reversal ratio
Control (Taxol only)	5.99	1.0
10 (marmesin)	> 2.50	
11 (decursinol)	> 2.50	
12 (decursinol angelate)	> 2.50	
13 (decursin)	> 2.50	
14 (prantschimgin)	1.03	5.8
15a	> 2.50	
15b	> 2.50	
15c	> 2.50	
15d	1.93	3.1
15e	0.166	36.0
15f	0.551	10.9
15g	> 2.50	
15h	> 2.50	
Verapamil	0.234	25.6

[a]MDR reversal activity of the compounds was evaluated at 5 μM on MES-SA/DX5 cells in the presence of Taxol. [b]All test compounds did not show any intrinsic cytotoxicity at 5 μM. [c]Mean of three independent experiments.

either by flash column chromatography using silica gel 60 (230-400 mesh Kieselgel 60) or by preparative thin layer chromatography using glass-backed silica gel plates (1 mm thickness) unless otherwise indicated. Addition- ally, thin-layer chromatography on 0.25 mm silica plates (E. Merck, silica gel 60 F254) was used to monitor reactions. The purity of the products was checked by reversed phase high-pressure liquid chromatography (RP-HPLC), which was performed either on Dionex Corp. HPLC system or on Waters Corp. HPLC system equipped with a UV detector set at 254 nm. The mobile phases used were A: H_2O containing 0.05% TFA, and B: CH_3CN. The HPLC employed an YMC Hydrosphere C_{18} (HS-302) column (5μ particle size, 12 nM pore size), 4.6 mm diameter × 150 mm with a flow rate of 1.0 mL/min.

2,4-Di-*tert*-butyl 1-formylphenyl carbonate (2). A suspension of 2,4-dihydroxy benzaldehyde **1** (2.0 g, 14.5 mmol), di-*tert*-butyl dicarbonate (12.6 g, 57.9 mmol) and potassium carbonate (4.0 g, 28.9 mmol) in diethyl ether (60 mL) was stirred at room temperature until completion. Reaction mixture was filtered and washed with diethyl ether. The combined filtrate was evaporated under reduced pressure. The resulting residue was quenched with water and diluted with ethyl acetate. The organic layer was separated, washed with brine and water, dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuo. The resulting crude product was purified by flash column chromatography (EtOAc:*n*-Hexane = 3:10) to yield **2** (4.4 g, 90%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.12 (s, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.23 (d, J = 1.8 Hz, 1H), 7.20 (s, 1H), 1.55 (d, J = 3 Hz, 18H).

2,4-Di-*tert*-butyl 1-hydroxymethylphenyl carbonate (3). $NaBH_4$ (15.3 mg, 403 mmol, in 0.27 mL H_2O) was added dropwise to a solution of **2** (130 mg, 384 mmol) in THF:H_2O (19:1, 1 mL) at 0 °C and stirred for 15 min. Reaction mixture was poured into ice-cold water and extracted with diethyl ether. Combined organic layers were washed with brine and water, dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuo. Purification by preparative TLC (EtOAc:*n*-Hexane = 3:7) gave alcohol **3** (93.7 mg, 70%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42 (d, J = 8.4 Hz, 1H), 7.07 (d, J = 2.4 Hz, 1H), 7.04 (dd, J = 2.1, 3.9 Hz, 1H), 4.56 (s, 2H), 2.37 (brs, 1H), 1.52 (s, 18H).

***tert*-Butyl 3-hydroxy-4-(3-methylbut-2-enyl) phenyl carbonate (4).** To a solution of alcohol **3** (1.29 g, 3.81 mmol) in THF (21 mL) was added 2-methyl-1-propenyl magnesium bromide (22.89 mL, 0.5 M in THF, 11.44 mmol) at 0 °C and stirred for 1 h. Reaction mixture was warmed to room temperature, and stirred for an additional 10 h. The reaction mixture was partitioned between 0.5 N HCl and diethyl ether. The combined organic layers were washed with brine and water, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography (EtOAc: *n*-Hexane = 1:9) yielded **4** (760 mg, 71%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.04 (d, J = 8.7 Hz, 1H), 6.64 (dd, J = 2.1, 8.4 Hz, 1H), 6.57 (d, J = 1.8 Hz, 1H), 5.84 (s, 1H), 5.26 (m, 1H), 3.26 (d, J = 7.2 Hz, 2H), 1.74 (s, 3H), 1.72 (s, 3H), 1.55 (s, 9H); MS (ESI) m/z 301 $(M+Na)^+$.

***tert*-Butyl 3-(benzyloxy)-4-(3-methylbut-2-enyl) phenyl carbonate (5).** A suspension of *tert*-butyl 3-hydroxy-4-(3-methylbut-2-enyl)phenyl carbonate **4** (0.60 g, 2.16 mmol), benzyl bromide (0.44 g, 2.59 mmol) and K_2CO_3 in DMF (10 mL) was stirred at room temperature for 12 h. Reaction mixture was quenched with ice-cold water and extracted with EtOAc. Combined extracts were washed with brine and water. Ethyl acetate layer was dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. Purification by column chromatography (EtOAc:*n*-Hexane = 1:9) provided **5** (0.65 g, 81.4%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38 (m, 5H), 7.14 (d, J = 8.4 Hz, 1H), 6.75 (s, 1H), 6.73 (d, J = 1.8 Hz, 1H), 5.31 (m, 1H), 5.06 (s, 2H), 3.35 (d, J = 7.5 Hz, 2H), 1.74 (s, 3H), 1.65 (s, 3H), 1.57 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.80, 152.01, 149.88, 136.90, 132.59, 129.49, 128.49, 127.94, 127.86, 127.31, 122.27, 113.06, 105.28, 83.38, 70.07, 28.25, 27.72, 25.75, 17.72; MS (ESI) m/z 391 $(M+Na)^+$.

3-(Benzyloxy)-4-(3-methylbut-2-enyl) phenol (6). To a solution of *tert*-butyl 3-(benzyloxy)-4-(3-methylbut-2-enyl) phenyl carbonate **5** (2.00 g, 5.43 mmol) in *n*-Butyl alcohol (200 mL) was added 4 M HCl solution (in dioxane, 70 mL) at room temperature and stirred until completion as indicated by TLC. Reaction mixture was quenched in ice-cold water, neutralized with aqueous sodium bicarbonate solution and diluted with a mixture of MeOH:CH_2Cl_2 (1:9). Separated organic layer, washed with brine and water. Dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (EtOAc:*n*-Hexane = 1.5:8.5) yielded 3-(benzyloxy)-4-(3-methylbut-2-enyl) phenol (1.32 g, 90.6%). ^{1}H NMR ($CDCl_3$, 300 MHz,) δ 7.36 (m, 5H), 6.99 (d, J = 8.1 Hz, 1H), 6.45 (d, J = 2.4 Hz, 1H), 6.35 (dd, J = 2.4, 8.1 Hz, 1H), 5.29 (m, 1H), 5.04 (s, 2H), 4.55 (brs, 1H), 3.29 (d, J = 7.5 Hz, 2H), 1.72 (s, 3H), 1.65 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.29, 154.65, 137.17, 132.06, 129.82, 128.48, 127.76, 127.22, 127.14, 122.94, 122.75, 106.85, 100.09, 69.90, 28.01, 25.77, 17.70; MS (ESI) m/z 269

$(M+H)^+$.

4-(Benzyloxy)-2-hydroxy-5-(3-methylbut-2-enyl) benzaldehyde (7). To a solution of **6** (523 mg, 1.95 mmol) and triethylorthoformate (1.45 g, 9.75 mmol) in benzene (25 mL) was added $AlCl_3$ (391 mg, 2.93 mmol) in portions at room temperature and stirred for 30 min. Reaction mixture was cooled to 0 °C and dropwise added a solution of 3 M HCl (28 mL). The resulting mixture was warmed to room temperature, extracted with ether and EtOAc. Combined organic layers were washed with brine and water, dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. Purification by flash column chromatography (EtOAc:*n*-Hexane = 1:9) formed **7** (279.6 mg, 48.4%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.45 (s, 1H), 9.72 (s, 1H), 7.42 (m, 5H), 7.27 (d, J = 2.4 Hz, 1H), 5.30 (m, 1H), 5.14 (s, 2H), 3.31 (d, J = 7.2 Hz, 2H), 1.78 (s, 3H), 1.66 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.54, 163.67, 163.08, 135.88, 133.46, 133.41, 128.66, 128.21, 127.27, 123.06, 121.62, 114.50, 99.71, 70.32, 27.71, 25.79, 17.74; MS (ESI) 297 $(M+H)^-$, 319 $(M+Na)^-$; Purity = 100% (as determined by RPHPLC, Rt = 22.63, 40%-100%, 30 min).

7-(Benzyloxy)-6-(3-methylbut-2-enyl)-2H-chromen-2-one (8). A solution of **7** (0.3 g, 1.0 mmol) and (carbethoxy-methylene)triphenylphosphorane (0.44 g, 1.27 mmol) in *N,N*-diethyl aniline (21 mL) was heated at 190 °C under argon for 5 h. The solution was cooled, poured into 1 L of 1.5 M HCl, and extracted 3 times with EtOAc. The combined EtOAc extracts were washed with 1.5 M HCl and brine, then dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The off-white solid residue was purified by flash column chromatography (EtOAc:*n*-Hexane = 3:7) providing 0.29 g (88.8%) of prenylated coumarin **8**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.66 (d, J = 9.6 Hz, 1H), 7.50-7.38 (m, 5H), 7.31 (s, 1H), 6.88 (s, 1H), 6.28 (d, J = 9.6 Hz, 1H), 5.35 (m, 1H), 5.2 (s, 2H), 3.43 (d, J = 7.2 Hz, 2H), 1.82 (s, 3H), 1.71 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.48, 159.57, 154.31, 143.57, 135.98, 133.63, 128.69, 128.22, 127.81, 127.60, 127.26, 121.42, 112.91, 112.10, 99.79, 70.39, 28.12, 25.80, 17.77; MS (ESI) m/z 321 $(M+H)^-$, 343 $(M+Na)^+$; Purity = 100% (as determined by RPHPLC, Rt = 21.17, 40%-100%, 30 min).

Demethylsuberosin (9). A solution of coumarin **8** (250 mg, 0.78 mmol) in EtOH (6 mL) was added to an aqueous slurry of Raney nickel (0.88 g) and the mixture was stirred for 3 h at room temperature under argon. The mixture was then rapidly filtered through a plug of Celite and concentrated. The residue was purified by flash chromatography (EtOAc:*n*-Hexane = 3:7) to yield pure 0.16 g (89.6%) of demethylsuberosin **9**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.65 (d, J = 9 Hz, 1H), 7.58 (s, 1H), 7.19 (s, 1H), 7.05 (s, 1H) 6.23 (d, J = 9.9 Hz, 1H), 5.32 (m, 1H), 3.37 (d, J = 7.2 Hz, 2H), 1.78 (s, 3H), 1.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.20, 158.42, 154.15, 144.12, 135.16, 128.31, 125.56, 120.96, 112.39, 112.31, 103.22, 28.52, 25.81, 17.87; MS (ESI) m/z 231 $(M+H)^+$, 253 $(M+Na)^+$; Purity = 100% (as determined by RPHPLC, Rt = 10.41, 40%-100%, 30 min).

Marmesin (10). Demethylsuberosin **9** (24 mg, 0.1 mmol) in $CHCl_3$ (1 mL) was added dropwise to an ice-cooled slurry of *m*-chloroperbenzoic acid (73 mg of 70% pure, 2 eq.) and $NaHCO_3$ (73 mg, 40 mmol) in $CHCl_3$ (3.3 mL). The mixture was stirred for 3 h at 0 °C and then quenched by slow addition of a solution of 219 mg $NaHSO_3$ in 3.3 mL water (Foams). The mixture was stirred for 20 min and then the layers were separated. The $CHCl_3$ layer was extracted twice with 0.2 M NaOH (to remove traces of over reduced demethylsuberosin from the previous step) and brine, then dried, and concentrated. The residue was purified by preparative TLC (EtOAc:*n*-Hexane = 3:7) gave pure marmesin as a colorless solid (20 mg, 79.6%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.58 (d, J = 9.9 Hz, 1H), 7.21 (s, 1H), 6.72 (s, 1H), 6.2 (d, J = 9.9 Hz, 1H), 4.73 (t, J = 8.85 Hz, 1H), 3.23-3.18 (m, 2H), 1.76 (s, 1H), 1.36 (s, 3H), 1.23 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.15, 161.42, 155.66, 143.66, 128.71, 123.39, 112.77, 112.30, 97.94, 91.10, 71.65, 29.48, 26.10, 24.25; MS (ESI) m/z 247 $(M+H)^-$, 269 $(M+Na)^-$; Purity = 100% (as determined by RPHPLC, Rt = 4.18, 40%-100%, 30 min).

Decursinol (11). A mixture of demethylsuberosin **9** (109 mg, 0.48 mmol), *m*-CPBA (128 mg, 77%, 0.57 mmol) and *p*-toluenesulfonic acid (4.6 mg) in chloroform (5 mL) was stirred at room temperature for 12 h. Reaction mixture was diluted with chloroform and washed with aqueous sodium bicarbonate and water. Organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc:*n*-Hexane = 1:3) affording pure decursinol as a colorless solid (84.5 mg, 71.5%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.58 (d, J = 9.6 Hz, 1H), 7.17 (s, 1H), 6.78 (s, 1H), 6.22 (d, J = 9.6 Hz, 1H), 3.87 (t, J = 5.1 Hz, 1H), 3.11 (dd, J = 4.65, 17.25 Hz, 1H), 2.83 (dd, J = 6.0, 16.8 Hz, 1H), 1.39 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.33, 156.44, 154.14, 143.13, 128.98, 116.42, 113.27, 112.92, 110.33, 104.74, 78.17, 69.11, 30.66, 25.01, 22.06; MS (ESI) m/z 247 $(M+H)^-$, 269 $(M+Na)^-$; Purity = 96 % (as determined by RPHPLC, Rt = 4.59, 40% - 100%, 30 min).

Decursin (12). A mixture of decursinol (51 mg, 0.21 mmol), DCC (47 mg, 0.23 mmol), angelic acid (21 mg, 0.21 mmol) and DMAP (2.5 mg, 0.02 mmol) in CH_2Cl_2 was stirred at room temperature for 26 h. The resulting precipitate of dicyclohexylurea was filtered and the solvent was removed in vacuo. Diethyl ether was added to the residue to precipitate additional urea and this was also filtered. The filtrate was washed with water and dried over anhydrous $MgSO_4$. The mixture was filtered and concentrated under reduced pressure. The crude product was purified by preparative TLC to yield white solid decursin **12** (26 mg, 38% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.59 (d, J = 9.3 Hz, 1H), 7.14 (s, 1H), 6.81 (s, 1H), 6.23 (d, J = 9.6 Hz, 1H), 5.08 (t, J = 5.1 Hz, 1H), 3.20 (dd, J = 16.8, 4.2 Hz, 1H), 2.88 (dd, J = 17.4, 5.1 Hz, 1H), 2.13 (d, J = 0.9 Hz, 3H), 1.86 (d, J = 1.2 Hz, 3H), 1.37 (s, 3H), 1.36 (s, 3H); MS (ESI) m/z 329 $(M+H)^+$; Purity = 100 % (as determined by RPHPLC, Rt = 15.71, 20%-100%, 30 min).

Decursinol angelate (13). LiHMDS was added to a stirred solution of decursinol (31 mg, 0.13 mmol) and DMAP (39 mg, 0.32 mmol) in THF at -40 °C. After the reaction mixture was stirred for 15 min at the same temperature, senecioyl chloride (75 mg, 0.63 mmol) was added. The solution was warmed to room temperature and stirred for 18 h. The reaction solution was quenched by the addition of saturated aqueous

sodium hydrogen carbonate and extracted with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$ and filtered, concentrated under reduced pressure. The residue was purified by preparative TLC to obtain white solid **13** (15 mg, 36% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.57 (d, J = 9.6 Hz, 1H), 7.14 (s, 1H), 6.79 (s, 1H), 6.22 (d, J = 9.6 Hz, 1H), 5.08 (t, J = 4.5 Hz, 1H), 4.2 (dd, J = 16.8, 4.2 Hz, 1H), 2.86 (dd, J = 17.7, 5.1 Hz, 1H), 2.14 (s, 3H), 1.88(s, 3H), 1.38 (s, 3H), 1.36 (s, 3H); MS (ESI) m/z 329 $(M+H)^-$; Purity = 100% (as determined by RPHPLC, Rt = 15.89, 20%-100%, 30 min).

Marmesin angelate (14). The marmesin (25 mg, 0.1 mmol), DCC (44 mg, 0.21 mmol) and angelic acid (20 mg, 0.2 mmol) were dissolved in the 6 mL of CH_2Cl_2. Then the reaction solution was heated at 30 °C for 24 h. The resulting precipitate of dicyclohexylurea was filtered and the solvent was evaporated under reduced pressure. Diethyl ether was added to the residue to precipitate additional urea and this was also filtered. The filtrate was concentrated and purified by preparative TLC to produce white solid **14** (16 mg, 48% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.59 (d, J = 9.6 Hz, 1H), 7.21 (s, 1H), 6.74 (s, 1H), 6.21 (d, J = 9.6 Hz, 1H), 5.13 (t, J = 9.6 Hz, 1H), 3.25-3.20 (m, 2H), 2.10 (s, 3H), 1.85 (s, 3H), 1.59 (s, 3H), 1.53 (s, 3H); MS (ESI) m/z 329 $(M+H)^+$; Purity = 100% (as determined by RPHPLC, Rt = 15.89, 20%-100%, 30 min).

3-Nitro-benzoic acid 6-(3-methyl-but-2-enyl)-2-oxo-2H-chromen-7-yl ester (15a). A solution of 7-hydroxy-6-(3-methyl-but-2-enyl)-chromen-2-one (30 mg, 0.13 mmol) in CH_2Cl_2 (3 mL) was added dropwise to an ice-cooled solution of 3-nitrobenzoyl chloride (27 mg, 0.14 mmol) and triethylamine (0.04 mL, 0.26 mmol). The mixture was stirred at room temperature for 18 h, basified with saturated aqueous $NaHCO_3$, extracted with dichloromethane, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc:*n*-Hexane = 1:5) to yield the product (18.6 mg, 62% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.04-9.03 (m, 1H), 8.55-8.51 (m, 1H), 7.79-7.69 (m, 3H), 7.39 (s , 1H), 7.19 (s, 1H), 6.42 (d, J = 9.3 Hz, 1H), 5.21 (t, J = 6.6 Hz, 1H), 3.32 (d, J = 6.6 Hz, 2H), 1.69 (s, 3H), 1.57 (s, 3H); MS (ESI) m/z 380 $(M+H)^-$; Purity = 96% (as determined by RPHPLC, Rt = 18.26, 40%-100%, 40min).

3,5-Dimethoxy-benzoic acid 6-(3-methyl-but-2-enyl)-2-oxo-2H-chromen-7-yl ester (15b). 7-hydroxy-6-(3-methyl-but-2-enyl)-chromen-2-one (30 mg, 0.13 mmol), 3,5-dimethoxy-benzoic acid (28 mg, 0.16 mmol), DCC (34 mg, 0.16 mmol) and DMAP (130 mg, 1.06 mmol) were dissolved in 5 mL of anhydrous CH_2Cl_2 and stirred at room temperature for 24 h. After evaporation of the solvent, the crude product was purified by flash column chromatography (MeOH:CH_2Cl_2 = 1:50) to yield the product (15.9 mg, 53% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.69 (d, J = 9.6 Hz, 1H), 7.36-7.33 (m, 3H), 7.17 (s, 1H), 6.75-6.74 (m, 1H), 6.39 (d, J = 9.6 Hz, 1H), 5.22 (t, J = 7.2 Hz, 1H), 3.87 (s, 6H), 3.31 (d, J = 7.2 Hz, 2H), 1.71 (s, 3H), 1.59 (s, 3H); MS (ESI) m/z 395 $(M+H)^+$; Purity = 100% (as determined by RPHPLC, Rt = 19.94, 40%-100%, 40 min).

4-Bromo-benzoic acid 6-(3-methyl-but-2-enyl)-2-oxo-2H-chromen-7-yl ester (15c). A solution of 7-hydroxy-6-(3-methyl-but-2-enyl)-chromen-2-one (31.7 mg, 0.14 mmol) in CH_2Cl_2 (3 mL) was added dropwise to an ice-cooled solution of 4-bromobenzyl chloride (33.26 mg, 0.15 mmol) and triethylamine (0.04 mL, 0.28 mmol). The mixture was stirred at room temperature for 18 h, basified with saturated aqueous $NaHCO_3$, extracted with dichloromethane, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc:*n*-Hexane = 1:5) to provide the product (23.4 mg, 74% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ8.08-8.04 (m, 1H), 7.68 (m, 4H), 7.36 (s, 1H), 7.17 (s, 1H), 6.40 (d, J = 9.6 Hz, 1H), 5.21 (t, J = 7.5 Hz, 1H), 3.30 (d, J = 7.5 Hz, 2H), 1.69 (s, 6H); MS (ESI) m/z 413 $(M+H)^-$; Purity = 97% (as determined by RPHPLC, Rt = 22.69, 40%-100%, 40 min).

6-(3-Methyl-but-2-enyl)-7-phenethyloxy-chromen-2-one (15d). A 2-bromoethylbenzene (0.26 mmol) was added to a stirred mixture of 7-hydroxy-6-(3-methyl-but-2-enyl)-chromen-2-one (40 mg, 0.18 mmol) and K_2CO_3 (73 mg, 0.53 mmol) in DMF (3 mL) at room temperature. The resulting mixture was vigorously stirred at room temperature for 18 h. When the starting material was exhausted, 15 mL of water was added and the mixture was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with water (10 mL) and then with brine (10 mL), dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography (EtOAc:*n*-Hexane = 1:10) to yield the product (48 mg, 83% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.59 (d, J = 9.6 Hz, 1H), 7.35-7.28 (m, 5H), 7.16 (s, 1H), 6.75 (s, 1H), 6.21 (d, J = 9.6 Hz, 1H), 5.24 (t, J = 7.2 Hz, 1H), 4.24 (t, J = 6.6 Hz, 2H), 3.28 (d, J = 7.2 Hz, 2H), 3.15 (t, J = 6.6 Hz, 2H), 1.75 (s, 3H), 1.68 (s, 3H); MS (ESI) m/z 357 $(M+Na)^-$, 335 $(M+H)^+$; Purity = 100% (as determined by RPHPLC, Rt = 23.28, 40%-100%, 40min).

6-(3-Methyl-but-2-enyl)-7-(pyridin-2-ylmethoxy)-chromen-2-one (15e). A 2-bromoethyl-pyridine (0.20 mmol) was added to a stirred mixture of 7-hydroxy-6-(3-methyl-but-2-enyl)-chromen-2-one (30 mg, 0.13 mmol) and K_2CO_3 (55 mg, 0.40 mmol) in DMF (3 mL) at room temperature. The resulting mixture was vigorously stirred at room temperature for 18 h. When the starting material was exhausted, 15 mL of water was added and the mixture was extracted with EtOAc (2×10 mL). The combined organic layers were washed with water (10 mL) and then with brine (10 mL), dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography (EtOAc:*n*-Hexane = 1:2) to give the product (24 mg, 79% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.65 (d, J = 4.2 Hz, 1H), 7.84 (t, J = 7.5 Hz, 1H), 7.63-7.56 (m, 2H), 7.36 (s, 1H), 7.23 (s, 1H), 6.84 (s, 1H), 6.24 (d, J = 9.6 Hz, 1H), 5.36-5.29 (m, 3H), 3.42 (d, J = 3.43 Hz, 2H), 1.78 (s, 3H), 1.70 (s, 3H); MS (ESI) m/z 344 $(M+Na)^+$, 322 $(M+H)^-$; Purity = 98% (as determined by RPHPLC, Rt = 9.21, 40%-100%, 40min).

6-(3-Methyl-but-2-enyl)-7-(4-nitro-benzyloxy)-chromen-2-one (15f). A 4-nitrobenzyl bromide (0.13 mmol) was added to a stirred mixture of 7-hydroxy-6-(3-methyl-but-2-enyl)-chromen-2-one (30 mg, 0.19 mmol) and K_2CO_3 (55 mg, 0.39 mmol) in DMF (2 mL) at room temperature. The resulting mixture was vigorously stirred at room temperature for 18 h. When the starting material was exhausted, 15 mL of water

was added and the mixture was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with water (10 mL) and then with brine (10 mL), dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography (EtOAc:*n*-Hexane = 1:5) to yield the product (39.5 mg, 82% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.26 (d, J = 8.27 Hz, 2H), 7.62 (d, J = 7.6 Hz, 2H), 7.80-6.45 (m, 4H), 5.82 (s, 2H), 5.20 (t, J = 9.6 Hz, 1H), 3.22 (d, J = 7.2 Hz, 2H), 1.75 (s, 3H), 1.68 (s, 3H); MS (ESI) m/z 366 $(M+H)^+$; Purity = 96% (as determined by RPHPLC, Rt = 20.7, 40%-100%, 40 min).

7-(Biphenyl-4-ylmethoxy)-6-(3-methyl-but-2-enyl)-chromen-2-one (15g). A 4-bromomethylbiphenyl (0.19 mmol) was added to a stirred mixture of 7-hydroxy-6-(3-methyl-but-2-enyl)-chromen-2-one (30 mg, 0.19 mmol) and K_2CO_3 (55 mg, 0.39 mmol) in DMF (2 mL) at room temperature. The resulting mixture was vigorously stirred at room temperature for 18 h. When the starting material was exhausted, 15 mL of water was added and the mixture was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with water (10 mL) and then with brine (10 mL), dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography (EtOAc:*n*-Hexane = 1:5) to give the product (40.3 mg, 78% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.80 (d, J = 9.6 Hz, 1H), 7.40-7.28 (m, 9H), 7.14 (s, 1H), 6.59 (s, 1H), 6.45 (d, J = 9.6 Hz, 1H), 5.80 (s, 2H), 5.20 (t, J = 6.6 Hz, 1H), 3.22 (d, J = 7.2 Hz, 2H), 1.75 (s, 3H), 1.68 (s, 3H); MS (ESI) m/z 367 $(M+H)^-$, 419 $(M+Na)^+$; Purity = 98% (as determined by RPHPLC, Rt = 26.66, 40%-100%, 40 min).

6-(3-Methyl-but-2-enyl)-7-(3-trifluoromethyl-benzyloxy)-chromen-2-one (15h) A 4-(trifluoromethyl) benzyl bromide (0.19 mmol) was added to a stirred mixture of 7-hydroxy-6-(3-methyl-but-2-enyl)-chromen-2-one (30 mg, 0.19 mmol) and K_2CO_3 (55 mg, 0.39 mmol) in DMF (2 mL) at room temperature. The resulting mixture was vigorously stirred at room temperature for 18 h. When the starting material was exhausted, 15 mL of water was added and the mixture was extracted with EtOAc (2×10 mL). The combined organic layers were washed with water (10 mL) and then with brine (10 mL), dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography (EtOAc:*n*-Hexane = 1:5) to form the product (47 mg, 92% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.80 (d, J = 9.6 Hz, 1H), 7.32 (d, J = 9.6 Hz, 1H), 7.38-7.12 (m, 4H), 6.59 (s, 1H), 6.45 (d, J = 9.6 Hz, 1H), 5.80 (s, 2H), 5.20 (t, J = 7.2 Hz, 1H), 3.22 (d, J = 7.2 Hz, 2H), 1.75 (s, 3H), 1.68 (s, 3H); MS (ESI) m/z 389 $(M+H)^+$; Purity = 98% (as determined by RPHPLC, Rt = 24.21, 40% -100%, 40 min).

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