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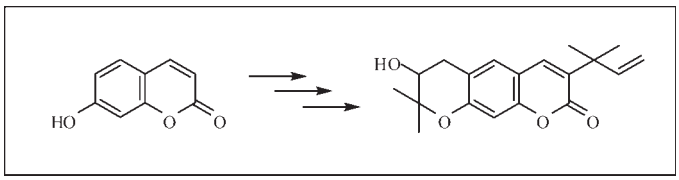

An improved preparation method of 3-(1,1-dimethylallyl)decursinol from inexpensive commercially available start material was described. In the cyclization of **13**, silica gel was used as catalyst to give **1** with high purity and satisfying yield.

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INTRODUCTION

3-(1,1-dimethylallyl)decursinol (**1**) was previously isolated from *Helietta longifoliata* Britt, a plant growing in South America, which has been used in Brazilian folk medicine for the treatment of various disease [1,2]. Compound **1** and it analogues (Fig. 1), such as (+)-decursinol (**2**), decursin (**3**), and decursinol angelate (**4**), constitute a class of dihydropyranocoumarin natural product, which has received considerable attention because of their diverse range of biological activities [2]. Both **3** and**4** have protein kinase C-related cytotoxic activity against various human cancer cells [3,4]. Compound **2** and **3** exhibited *in vitro* activities toward acetylcholinesterase, as well as the two compounds could excellently improve scopolamine-induced amnesia *in vivo*. Additionally, these dihydropyranocoumarin was found to exhibit anti-*Helicobacter pylori* activity and strong analgestic activity [5].

As the resource of **1** is restricted to the species of *Helietta longifoliata*, the detailed biological investigation has not been successful so far. To explore the potential biological activities of **1** and its derivatives, a reliable preparing procedure in large scale was needed. Rosario has semisynthesized the compound of **1** in milligram scale; nevertheless, the resource of start material was also limited [6].

Herein, an improved preparing procedure, staring with inexpensive, commercially available 7-hydroxy-2*H*-chromen-2-one (**5**), was reported (Scheme 1). In the process, compound **9**was deprotected in the presence of active Ni with almost quantitative yield. The cyclization of compound **13** could be promoted by silica gel to obtain compound **1**, and the later was purified by simple crystallization rather than chromatograph.

RESULTS AND DISCUSSION

The hydroxyl in compound **5** was protected by benzyl in the presence of potassium carbonate to give **6**. The latter was treated with sodium methoxide in refluxing methanol, and then reacted with 1-bromo-3-methylbut-2-ene to obtain compound **8**. On heating in refluxing diethylaniline, **8** smoothly rearranged, resulting in prenyl substitution at the free C-3 position with concomitant relactonisation to produce **9** [7].

In the ref. [7], the benzyl group was removed in the presence of trichloroborane; nevertheless, our attempt to scale up the reaction in several hundred grams was failed. The reason was trichloroborane, a strong Lewis-acid, could induce some side-reaction. Hydrogenation of **9** to remove the benzyl, using Raney Ni as catalyst afforded the compound **10**in quantitative yield, although trace of by-product was formed.

The free hydroxyl of **10** was prenylated to furnish the key intermediate **11**, sigmatropic rearrangement of which in refluxing diethylaniline gave the compound **12**. Epoxidation of **12** in dichloromethane gave the unstable intermediate**13**, which could be conversed to compound **1** in the presence of silica gel *in situ*, and the product can be purified conveniently by crystallization in ethyl acetate.

EXPERIMENTAL

All solvents and reagents were purchased from the suppliers and used without further purification. ^{1}H NMR spectra were recorded in deuteriochloroform or DMSO-d_6 at room temperature on a Bruker AMX-400/600 at 400 MHz using TMS as an internal standard. The mass spectrum was recorded on a

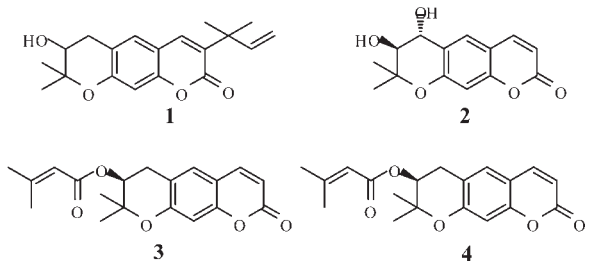


Figure 1. Structures of **1** and its analogues.

Finnigan MAT-95/711 spectrometer. Melting points were measured on a Buchi-510 melting point apparatus, which are uncorrected. TLC analyses were performed on Merck silica gel 60 F_{254} plate.

7-(Benzyloxy)-2*H*-chromen-2-one (6). 1.0 kg (6.18 mol) compound **5** was added to the mixture of 2.0 kg (14.47 mol) K_2CO_3, 0.1 kg KI (0.6 mol), and 12 L acetone and then, 0.86 kg (6.78 mol) benzyl chloride was added. The resulted mixture was heated to reflux for 4 h, cooled to room temperature, filtrated, and the filtration was concentrated under decreased pressure. The residue was dissolved in 20 L CH_2Cl_2, washed with saturated NH_4Cl solution and H_2O, dried over Na_2SO_4, concentrated, and filtrated to obtain 1.5 kg white solid **6**, yield 96.4%, mp 151–154°, ref. [8] 153–155°. The spectroscopic data correspond to those reported in the ref. [8].

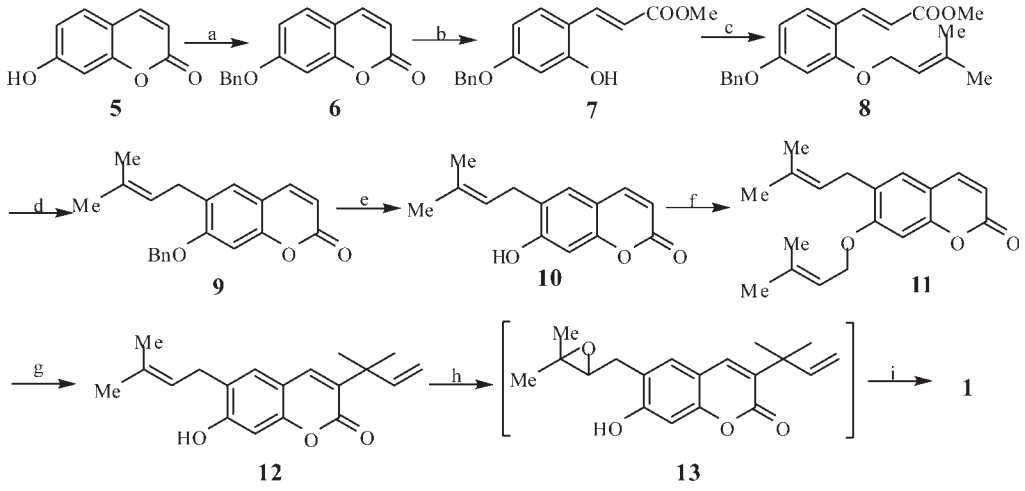
Methyl 3-(4-(benzyloxy)-2-hydroxyphenyl)acrylate (7). 1.5 kg (6 mol) **6** was dissolved in the mixture of 16 L methanol and 2.0 kg (37 mol) sodium methylate. The resulted mixture was heated to reflux for 6 h, cooled to room temperature, added to 40 L of 2.6*M* hydrochloric acid with stirring at 0°, filtrated to obtain white solid. The solid was washed with H_2O, dried at 60° to obtain 1.27 kg **7** as white solid, yield 75%, mp 182–183°, ref. [7] 184.5–186°; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.66 (s, 3H), 5.06 (s, 2H), 6.45 (d, J = 16 Hz, 1H), 6.50 (s, 1H), 6.52 (d, J = 7.2 Hz, 1H), 7.32–7.43 (m, 5H), 7.52 (d, J = 7.2 Hz, 1H), 7.77 (d, J = 16 Hz, 1H).

Methyl 3-(4-(benzyloxy)-2-(3-methylbut-2-enyloxy) phenyl) acrylate (8). 1.27 kg (4.45 mol) compound **7** was added to the suspension of 1.24 kg (9.27 mol) K_2CO_3 and 120 g (0.73 mol) KI in 15 L acetone, then the 620 mL (5.34 mol) 1-bromo-3-methylbut-2-ene was added dropwise. The resulted mixture was stirred at room temperature for 3 h, filtrated, and the filtration was concentrated. The obtained residue was dissolved in 8 L CH_2Cl_2, and the organic layer was washed by H_2O and saturated brine, dried over Na_2SO_4, filtrated, and concentrated to oil. The oil was stirred in 3 L petroleum ether for 2 h, filtrated to obtain 1.2 kg **8** as white solid, yield 77%, mp 62–63°, ref. [7] 59–61°; ^{1}H NMR (300 MHz, deuteriochloroform): δ 1.76 (s, 3H), 1.82 (s, 3H), 3.79 (s, 3H), 4.55 (d, J = 7.2 Hz, 2H), 5.06 (s, 2H), 5.48 (m, 1H), 6.42 (d, J = 16 Hz, 1H), 6.55 (m, 2H), 7.37 (m, 6H), 7.63 (d, J = 9 Hz, 1H).

7-(Benzyloxy)-6-(3-methylbut-2-enyl)-2*H*-chromen-2-one (9). 400 g (1.1 mol) **8** was dissolved in 2 L *N*,*N*-diethyl-benzenamine in 5 L reactor equipped with water segregator. The solvent was heated to reflux under N_2. During the removing of methanol, the temperature of reaction mixture developed from 202° to 226°, reflux for another 3 h, cooled to room temperature. The mixture was added into 10 L of 2*M* hydrochloric acid, extracted with ethyl acetate three times. The combined organic layer was washed by saturated brine, dried over Na_2SO_4, concentrated to obtain slurry, filtrated to obtain 713 g **9** as white solid, yield 65%, mp 102–103°, ref. [7] 104–104.5°; ^{1}H NMR (300 MHz, deuteriochloroform): δ 1.66 (s, 3H), 1.76 (s, 3H), 3.37 (d, J = 7.2 Hz, 2H), 5.06 (s, 2H), 5.30 (m, 1H), 6.25 (d, J = 9 Hz, 1H), 6.83 (s, 1H), 7.21 (s, 1H), 7.42 (m, 5H,), 7.63 (d, J = 9 Hz, 1H).

7-Hydroxy-6-(3-methylbut-2-enyl)-2*H*-chromen-2-one (10). 355 g (1.1 mol) compound **9** was dissolved in the mixture of 3.5 L ethanol, 500 mL H_2O, and 10 g Raney Ni, the resulted suspension was stirred under H_2 at room temperature for 24 h, filtrated, the filtration was concentrated to obtain white solid 250 g **10**, yield 98%, mp 133–135°, ref. [7] 133–135°; ^{1}H NMR (300 MHz, deuteriochloroform): δ 1.75 (s, 3H), 1.79 (s, 3H), 3.38 (d, J = 7.5 Hz, 2H), 5.34 (m, 1H),

Scheme 1. Conditions: (a) benzyl chloride, K_2CO_3, KI, acetone, reflux, 96%; (b) sodium methoxide, methanol, 75%; (c) 1-bromo-3-methybut-2-ene, K_2CO_3, KI, acetone, r.t., 77%; (d) *N*,*N*-diethylbenzenamine, reflux, 65%; (e) H_2, Riney-Ni, ethanol, H_2O; (f) 1-bromo-3-methylbut-2-ene, K_2CO_3, KI, acetone, r.t., 70%; (g) *N*,*N*-diethylbenzenamine, reflux, 32%; (h) m-CPBA, CH_2Cl_2, 0°C; (i) silica gel, 0°C, 75%.



6.23 (d, $J = 9$ Hz, 1H), 7.00 (s, 1H), 7.11 (s, 1H), 7.42 (m, 5H), 7.66 (d, $J = 9$ Hz, 1H).

6-(3-Methylbut-2-enyl)-7-(3-methylbut-2-enyloxy)-2*H*-chromen-2-one (11). 77 g (4.45 mol) compound **10** was added to the suspension of 120 g (0.95 mol) K_2CO_3 and 5 g (30 mmol) KI in 1 L acetone, then the 60 mL (0.5 mol) 1-bromo-3-methylbut-2-ene was added dropwise. The resulted mixture was stirred at room temperature for 3 h, filtrated, and the filtration was concentrated. The obtained residue was dissolved in 0.5 L CH_2Cl_2, and the organic layer was washed by H_2O and saturated brine, dried over Na_2SO_4, filtrated, and concentrated to oil. The oil was stirred in 300 mL petroleum ether for 2 h, filtrated to obtain 70 g **11** as white solid, yield 70%, mp 76–78°, ref. [7] 78–79°; ^{1}H NMR (300 MHz, deuteriochloroform): δ 1.71 (s, 3H), 1.77 (s, 6H), 1.78 (s, 3H), 3.38 (d, $J = 7.5$ Hz, 2H), 4.63 (d, $J = 7.5$ Hz, 2H), 5.30 (m, 1H), 5.46 (m, 1H), 6.76 (s, 1H), 7.17 (s, 1H), 7.61 (d, $J = 9$ Hz, 1H).

7-Hydroxy-6-(3-methylbut-2-enyl)-3-(2-methylbut-3-en-2-yl)-2*H*-chromen-2-one (12). 82 g (1.1 mol) compound **11** was dissolved in 0.5 L *N*,*N*-diethylbenzenamine in 5 L reactor equipped with water segregator. The solvent was heated to reflux under N_2. During the removing of methanol, the temperature of reaction mixture developed from 202° to 226°, reflux for another 3 h, cooled to room temperature. The mixture was added into 500 mL of 2*M* hydrochloric acid, extracted with ethyl acetate three times. The combined organic layer was washed by saturated brine, dried over Na_2SO_4, concentrated to obtain residue, which was purified on silica gel column (petroleum ether:ethyl acetate = 20:1) filtrated to obtain 27.5 g **12** as white solid, yield 32%, mp 163–165°, ref. [7] 181–183°; ^{1}H NMR (300 MHz, deuteriochloroform): δ 1.47 (s, 6H), 1.77 (s, 3H), 1.79 (s, 3H), 3.38 (d, $J = 7.5$ Hz, 2H), 5.04 (dd, 1H), 5.30 (m, 1H), 6.08–6.21 (m, 2H), 6.84 (s, 1H), 7.17 (s, 1H), 7.50 (s, 1H).

(±)-3-(1,1-Dimethylallyl)decursinol (1). 5 g (16.7 mmol) compound **12** was dissolved in 80 mL ethyl ether, to which 4.3 g (21.2 mmol) m-CPBA was added in portions at 0°C, the mixture was stirred for 6 h at room temperature. The reaction was monitored by TLC. When compound **12** was consumed up, 10 g silica gel was added to the resulted mixture at 0°, stirred for another 1 h. The mixture was filtrated, and the filtration was washed by saturated $NaHCO_3$ and H_2O, dried over Na_2SO_4, concentrated to obtain crude product, which was crystallized in ethyl acetate to give 3.7 g **1** as white solid, yield 70%, mp 182–183°, ref. [6] 181–183°; ms: m/z 337 (M^++Na); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.38 (s, 3H), 1.47 (s, 6H), 2.82 (dd, $J = 14$, 6 Hz, 1H), 3.10 (dd, $J = 14$, 6 Hz, 1H), 3.85 (m, 1H), 1.79 (s, 3H), 3.38 (d, $J = 7.5$ Hz, 2H), 5.06 (m, 2H), 6.17 (dd, $J = 17$, 12 Hz, 1H), 6.74 (s, 1H), 7.15 (s, 1H), 7.47 (s, 1H).

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