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IMPROVED TOTAL SYNTHESIS OF RACEMIC RUTAMARIN

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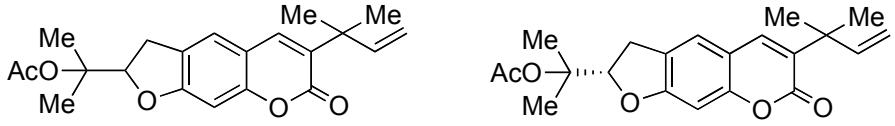
Abstract – An improved, convenient and cost-effective process, using 2,4-dihydroxybenzaldehyde **2** as starting material for (±)-rutamarin **1**, is described. The overall yield of **1** is 44% in eight steps, requiring no chromatographic purification.

(±)-Rutamarin **1**, 3-subtsituted 6,7-furanocoumarin, previously isolated from the *Ruta graveolens L.*, has spasmogenic inhibiting effect on isolated smooth muscle organs.[1,2] (±)-Rutamarin **1** also showed a selective affinity to the cannabinoid receptor type-2 (CB2) with a *K*i of 7.4±0.6 μM.[3] The significant inhibitory effect against several tumor cell lines has been described.[4-6] Recently, it was reported that (+)-rutamarin (Figure 1) had the strongly sensitization effect on the insulin in the GLUT4 translocation assay, indicating its promising anti-diabetic activity.[7] The broad, potent biological activities of (±)-rutamarin **1** indicate that it can be the lead compound in the further development of novel therapeutic agent.

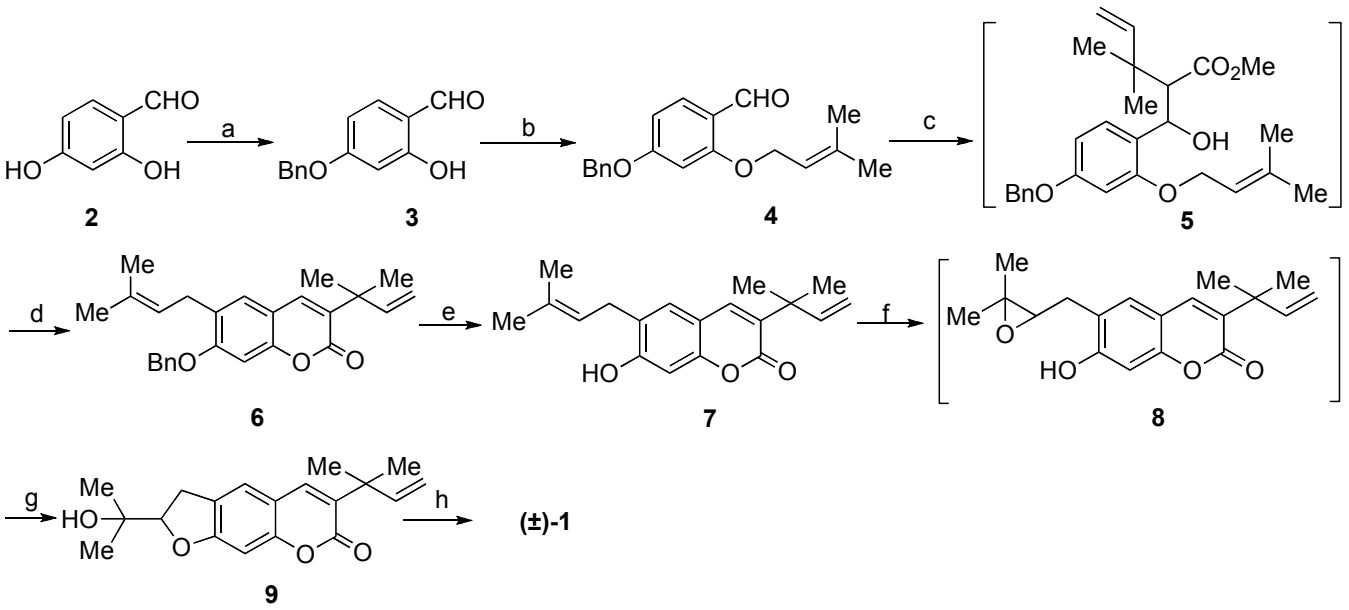


(±)-rutamarin 1 **(+)-rutamarin 1**

Figure 1. Structures of racemic rutamarin and (+)-rutamarin

Several papers have been published regarding the synthesis of **1** and intermediate **7**.[7-12] Massanet and coworkers[10] originally semi-synthesized racemic-rutamarin **1** from **7**, though the cyclization step needed the complex chromatography column of basic alumina. We have previously improved the method of

Rosario[9] to prepare **7**, but the yield is still unsatisfying (8% over seven steps).[8] Cairns gave rise to the coumarin ring system of **7** from the allyl ether in a tandem manner.[12] (+)-Rutamarin has also been synthesized by Zhang and coworkers.[7] The above-mentioned processes, requiring complex chromatographic purifications, are not suitable for preparing (±)-rutamarin **1** in large scale.



Scheme 1. *Reagents and conditions*: a) benzyl chloride, $NaHCO_3$, KI, 60 °C, 85%; b) 1-bromo-3-methyl-2-butene, K_2CO_3, KI, DMF, rt, 95%; c) diisopropylamine, *n*-butyllithium, 3, 3-dimethylpentanoic acid methyl ester, -30 °C; d) *N,N*-diethylaniline, reflux, 90% over two steps; e) $AlCl_3$, *N,N*-diethylaniline, 0 °C, 70%; f) *m*-CPBA, CH_2Cl_2, 0 °C; g) DMAP, rt, 91% over two steps; h) Ac_2O, *p*-TsOH, rt, 95%.

Herein, an improved procedure to make (±)-rutamarin **1** with satisfying yield, starting from 2,4-dihydroxybenzoaldehyde, was described (Scheme 1). The new procedure, no need to use chromatographic purifications and expensive reagent, makes it possible to get **1** at kg scale with convenience and low cost.

Compound **2**, 2,4-dihydroxybenzaldehyde, was benzylated to give compound **3** with satisfying yield, in the presence of sodium bicarbonate and potassium iodide. Compound **3** was then alkylated to give compound **4** with almost quantitative yield.

3,3-dimethylpentanoic acid methyl ester was treated with the solution of lithium diisopropylamine (LDA), followed by condensation with **4** at -30 °C to give intermediate **5**. Other basic reagents, such as sodium hydride and *n*-butyllithium, worked in this classic condensation reaction with relatively lower yield. Crude **5** was directly used in the next one-pot reaction without further purification.

Intermediate **5** was heated to 215 °C in refluxed *N,N*-diethylaniline to give compound **6** with satisfying yield (90% over two steps). The one-pot step included three chemical conversations: the rearrangement of isopentenyl from the oxygen atom at C-2 position to C-5 position;[8,9] the dehydration to form the double bond conjugating with the benzene; the cyclization to construct the lactone moity with the removal of

methanol. This one-pot method shows obviously merits, such as high yield, free of chromatography, convenient operations, comparing to the reported method.

Many reaction conditions have been tried to remove the benzyl on the oxygen atom at C-4 position. The double bond will be reduced during hydrogenation of compound **6** with Pd/C or active-Ni as catalyst. When Lewis acids, such as BCl_3 and BBr_3, were used to perform this debenzylation, a lot of byproducts were generated. $AlCl_3$ is successfully found to give the compound **7** as white solid at yield of 70% after crystallization.

In the reported process, epoxidation of **7** with *m*-chloroperbenzoic acid (*m*-CPBA) gave the unstable intermediate **8**, which could be selectively conversed to compound **9** by chromatography column of basic alumina.[10] It is obviously that the process is not suitable for preparing in large scale. We found that if a weak base, 4-*N,N*-dimethylaminopyridine (DMAP) was directly added to the reaction solution when the epoxidation reaction completed, intermediate **8** was subsequently cyclized to give compound **9** *in situ*. The acetylation of **9** was performed in acetic anhydride to give (±)-rutamarin **1** with almost quantitative yield.

In summary, an improved process for (±)-rutamarin **1** was provided at total yield of 44% over eight steps. The key intermediate **6** was conveniently prepared by the newly developed one-pot process including rearrangement, dehydration and cyclization. Epoxidation of **7** and following cyclization *in situ* gave **9** without any chromatography purification. This efficient process can give kg-scale (±)-rutamarin **1** with low cost.

EXPERIMENTAL

All commercially available materials and solvents were used as received without any further purification. ^{1}H NMR spectra were recorded in $CDCl_3$ at room temperature on a Bruker AMX/300 using TMS as an internal standard. ^{13}C NMR spectra were obtained from a Gemini-300 spectrometer in $CDCl_3$ at room temperature. The chemical-shift scale is based on internal TMS. The mass spectrum was recorded on Finnigan MAT-95/97 or Finnigan MAT-95 XP spectrometer. Melting points were measured on a Buchi-510 melting point apparatus, which are uncorrected. TLC analyses were performed on Merck silica gel 60 F254 plate.

4-Benzyloxy-2-hydroxybenzaldehyde (3)

To a solution of 2,4-dihydroxybenzaldehyde **2** (743 g, 5.38 mol) in MeCN (3.7 L), $NaHCO_3$ (903 g, 10.6 mol), KI (89 g, 0.5 mol) and benzyl chloride (680 g, 5.38 mol) were added. The mixture was stirred at 60 °C for 12 h. The resulted mixture was filtrated and the filtrate was concentrated to give the residue. The residue was dissolved in EtOH (1.5 L), cooled to 5 °C, filtrated and dried in oven to obtain compound **3** as white solid (1043 g, 85%). Mp 73–75 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ5.11 (s, 2H),

6.51 (d, 1H, *J* = 2.1 Hz), 6.60 (dd, 1H, *J* = 1.8 Hz, 2.4 Hz), 7.41 (m, 6H), 9.72 (s, 1H), 11.48 (s, 1H); ESI-MS (m/z) 229 $[M + H]^+$.

4-Benzyloxy-2-(3-methylbut-2-enyloxy)benzaldehyde (4)

To the solution of compound **3** (1025 g, 4.4 mol) in DMF (4 L), K_2CO_3 (737 g, 5.3 mol), KI (74 g, 0.4 mol) and 1-bromo-3-methyl-2-butene (696 g, 4.62 mol) were added. The mixture was stirred at 20 °C for 3 h. The resulted mixture was poured into water, filtrated, and the cake was washed with water for two times, dried in oven to obtain compound **4** as white solid (1253 g, 95%). Mp 63–65 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ1.74 (s, 3H), 1.80 (s, 3H), 4.57 (d, J = 6.6 Hz, 2H), 5.12 (s, 2H), 5.48 (t, 1H), 6.53 (d, J = 2.1 Hz, 1H), 7.37 (m, 5H), 7.80 (d, 1H), 10.32 (s, 1H); ESI-MS (m/z) 319 $[M + Na]^+$.

4-Benzyloxy-6-(3-methylbut-2-enyl)-3-(2-methylbut-3-en-2-yl)-2*H*-chromen-2-one (6)

To the solution of diisopropylamine (20.5 g, 0.2 mol) in anhydrous THF (250 mL), the solution of *n*-butyllithium in hexane (84 ml, 0.2 mol) was added carefully at -30 °C. The mixture was stirred for 10 min under -30 °C. Then 3, 3-dimethylpentanoic acid methyl ester (26.4 g, 0.19 mol) was added, and the resulted mixture was stirred for 90 min. Then the pre-cooled solution of **4** (50 g, 0.17 mol) in THF (100 mL) was added dropwise, and the stirring continued at -30 °C for 2 h. Saturated aqueous NH_4Cl (200 mL) solution was added, and ethyl acetate was added. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated under vacuum to obtain the crude **5** as colorless oil. The solution of crude **5** in *N,N*-diethylaniline (200 mL) was heated to reflux under nitrogen atmosphere for 3 h, cooled to room temperature, and poured into hydrochloric acid (140 mL). The resulted mixture was extracted with EtOAc for three times. The combined organic layer was washed by saturated brine, dried over Na_2SO_4, concentrated to obtain residue, which was purified by crystallisation in ethanol to obtain **6** as yellow solid (59 g, 90%). Mp 72–75 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.49 (s, 6H), 1.67(s, 3H), 1.77(s, 3H), 3.36(d, *J* = 9 Hz, 2H), 5.04(d, *J* = 9 Hz, 1H)i, 5.10(s, 1H), 5.13(s, 2H), 5.30(t, 1H), 6.19(m, 1H), 6.80(s, 1H), 7.19(s, 1H), 7.39(m, 5H), 7.51(s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 17.73, 25.81, 26.07, 28.05, 40.29, 70.16, 98.97, 111.97, 112.33, 121.56, 127.14, 127.29, 127.43, 128.07, 128.60, 131.36, 133.41, 136.07, 137.95, 145.58, 153.25, 158.60, 160.24; ESI-MS (*m/z*) 389 $[M + H]^+$; HRMS: *m/z* calcd for $C_{26}H_{28}O_3Na$ (M+Na) 411.1936, found 411.1946.

7-Hydroxy-6-(3-methylbut-2-enyl)-3-(2-methylbut-3-en-2-yl)-2*H*-chromen-2-one (7)

To a stirred solution of $AlCl_3$ (670 g, 5.1 mol) in CH_2Cl_2 (3 L), *N,N*-diethylaniline (748 g, 6.2 mol) was added under -10 °C, then the pre-cooled solution of **6** (390 g, 1 mol) in CH_2Cl_2 (3 L) was added. The mixture was stirred at 0 °C for 1 h, and poured into 400 ml of cool hydrochloric acid. The organic layer was washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated under vacuum to give the residue. The residue was crystallized in hexane to give compound **7** as yellow solid (209 g 70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.47 (s, 6H), 1.77 (s, 3H) , 1.79 (s, 3H), 3.38 (d, 2H, *J* = 7.5 Hz), 5.04–5.10

(m, 2H), 5.31 (m, 1H), 6.08~6.21 (m, 2H), 6.84 (s, 1H), 7.17 (s, 1H), 7.50 (s, 1H); ESI-MS (*m/z*) 321 [M + Na]$^+$.

2,3-Dihydro-2-(2-hydroxypropan-2-yl)-6-(2-methylbut-3-en-2-yl)furo[3,2-g]chromen-7-one (9).

To the solution of compound **7** (117 g, 0.39 mol) in CH_2Cl_2 (1 L), *m*-CPBA (67.5 g, 0.39 mol) was added in portions at 0 °C, and the mixture was stirred at room temperature for 1 h. DMAP (271 g, 0.88 mol) was added, and the resulted mixture was stirred at room temperature for 16 h. Then the mixture was washed with saturated Na_2SO_3, 0.5 N NaOH, saturated brine, dried over Na_2SO_4, concentrated to give residue. The residue was stirred in petroleum ether, filtrated to obtain compound **9** as white solid (112 g, 91%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.47 (s, 6H), 1.75 (s, 3H), 1.79 (s, 3H), 3.20 (m, 2H), 4.71 (m, 1H), 5.04–5.10 (m, 2H), 6.12–6.21 (m, 1H), 6.71 (s, 1H), 7.19 (s, 1H), 7.48 (s, 1H); ESI-MS (*m/z*) 337 [M + Na]$^+$.

(±)-Rutamarin (1)

A solution of compound **9** (500 g, 1.6 mol) and *p*-toluensulfonic acid (30 g, 0.17 mol) in acetic anhydride (3 L) was stirred for 2 h at room temperature. Then ice water was added and the stirring was continued for 1 h. The suspension was filtrated, and the cake was washed with water to obtain (±)-rutamarin **1** as white solid (543 g, 95%). ^{1}H NMR ($CDCl_3$, 300 MHz) : δ 1.47 (s, 6H), 1.50 (s, 3H), 1.55 (s, 3H), 1.98 (s, 3H), 3.20 (m, 2H), 4.71 (m, 1H), 5.04–5.10 (m, 3H), 6.12–6.21 (m, 1H), 6.71 (s, 1H), 7.18 (s, 1H), 7.47 (s, 1H); ESI-MS (*m/z*) 379 [M + Na]$^+$.

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