

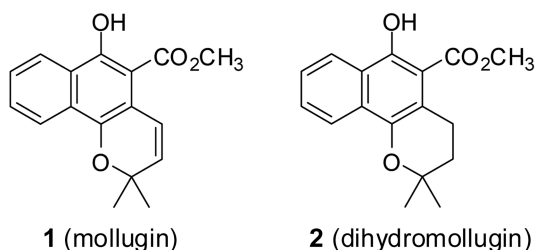
## A Facile Synthesis of Mollugin

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Mollugin (**1**) is one of the major 2*H*-naphtho[1,2-*b*]pyran component isolated from Rubiaceae species such as *Putoria calabrica* and *Rubia cordifolia* L. (Rubiaceae),<sup>1</sup> a herbal medicine used for the treatment of arthritis, dysmenorrhea, hematorrhea, and hemostasis, as a tonic, and for wound healing in China<sup>2</sup> and used for menstrual pain, rheumatism, and urinary disorders in India.<sup>3</sup> Antitumor activity,<sup>4</sup> anti-mutagenic activity,<sup>5</sup> antiviral activity against hepatitis B virus,<sup>1c</sup> and strong inhibitory activity on arachidonic acid and collagen-induced platelet aggregation<sup>6</sup> of mollugin have been reported. In addition, mollugin inhibited cell adhesion between angioendothelial cells and lymphocytes thus having potentials for cosmetic additives with hair growth stimulant activity<sup>7</sup> and anti-aging activity.<sup>8</sup>



The intriguing structure and the various biological activities of **1** have led to introduce a series of total synthesis. The first synthesis was achieved from 1,4-dihydroxy-2-naphthoic acid and 3-chloro-3-methylbut-1-yne in 23% over all yield.<sup>9</sup> Reaction of methyl 1,4-dihydroxy-2-naphthoate and 3-methylbut-1-en-3-ol afforded dihydromollugin (**2**),<sup>10</sup> which was then dehydrogenated by DDQ to lead **1**, but no yield was given. Lumb and Trauner employed oxa 6*π*-electrocyclization of 2-methoxycarbonyl-3-prenyl-1,4-naphthoquinone.<sup>11</sup> Recently, Claessens, *et al.* reported a 9-step synthetic sequence from 1,4-naphthoquinone *via* selective prenylation and oxa 6*π*-electrocyclization.<sup>12</sup> Biosynthesis of **1** by using *Galium mollugo* L. cell cultures has also been reported.<sup>13</sup>

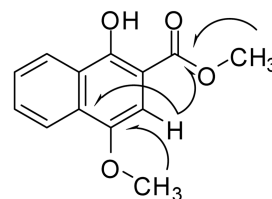
On the other hand, 2,2-dimethylchromen (2,2-dimethyl-2*H*-1-benzopyran) ring has been constructed by a couple of synthetic methods. The older methods included reaction of coumarins with methylmagnesium halides,<sup>14</sup> reaction of phenols with 2-methylbut-3-yn-2-ol,<sup>15</sup> pyridine-catalyzed condensation of phenols with 3-methyl-2-butenal diacetal.<sup>16</sup> However, pyridine-catalyzed condensation limited only to

phenols with *meta*-pair hydroxy groups.<sup>16b</sup> Recently, phenylboronic acid has been used for the *ortho*-specific attack on phenols by  $\alpha,\beta$ -unsaturated aldehydes and ketones to lead to a protonated quinonemethides which are readily undergone electrocyclization to construct benzopyran skeletons.<sup>17</sup> Such methods have also been applied to construct 2*H*-naphtho[1,2-*b*]pyran skeleton.<sup>16c,17</sup>

As a part of our continuing interest in the establishment of synthetic method for nature-originated biologically active compounds<sup>18</sup> and of pursuing further biological properties of mollugin on experimental animals, a practical synthetic method is required to secure sufficient quantity of mollugin. We, herein, described a facile synthesis of **1** from readily available 1,4-dihydroxy-2-naphthoic acid and 3-methyl-2-butenal by an intermolecular phenylboronic acid-mediated cyclization.

We reasoned that the intermolecular phenylboronic acid-mediated cyclization of **4a** with 3-methyl-2-butenal would afford mollugin. We thus attempted direct esterification of **3** with CH<sub>3</sub>OH in the presence of H<sub>2</sub>SO<sub>4</sub>. The reaction, however, afforded methyl 1-hydroxy-4-methoxynaphthoate (**4b**) and 4-methoxy-1-hydroxy-2-naphthoic acid (**4c**) instead of desired **4a** in a ratio of 98:2 with 94% conversion. Subsequent AlCl<sub>3</sub>-catalyzed demethylation of **4b** afforded desired methyl 1,4-dihydroxy-2-naphthoate (**4a**) in quantitative yield. Although **4a** could be prepared by selective esterification of **3** by employing previously reported method,<sup>19</sup> the present method is more cost-effective. Subsequent intermolecular phenylboronic acid-mediated cyclization of **4a** with 3-methyl-2-butenal yielded mollugin (**1**) in 87% yield. Structures of **4b** were confirmed by spectroscopic methods including HMBC (Figure 1).

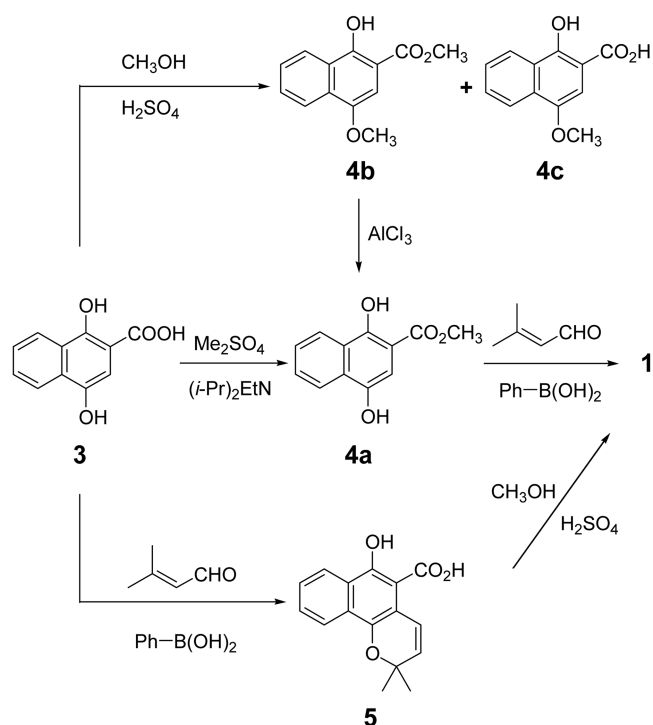
Alternatively, direct cyclization of **3** was also pursued to afford the corresponding 6-hydroxy-2,2-dimethyl-2*H*-



**Figure 1.** Selected <sup>1</sup>H-<sup>13</sup>C long-range correlations in HMBC spectrum of **4b**.

naphtho[1,2-*b*]pyran-5-carboxylic acid (**5**) in 89% yield, which was then converted to mollugin by conventional esterification in 98% yield.

Catalytic hydrogenation of **1** by previously reported method<sup>1c</sup> quantitatively afforded corresponding dihydro-mollugin (**2**).



In conclusion, mollugin was prepared from 1,4-dihydroxy-2-naphthoic acid and 3-methyl-2-butenal by intermolecular phenylboronic acid-mediated cyclization. Alternative 2-step synthesis of mollugin from 1,4-dihydroxy-2-naphthoic acid was also successful. Studies on the synthesis of mollugin derivatives and their biological properties are in progress.

### Experimental Section

Melting points were determined using a Fischer-Jones melting points apparatus and are not corrected. IR spectra were obtained using a Perkin-Elmer 1330 spectrophotometer. NMR spectra were obtained using a Bruker-250 spectrometer 250 MHz for <sup>1</sup>H NMR and 62.5 MHz for <sup>13</sup>C NMR and are reported as ppm from the internal standard TMS. Chemicals and solvents were commercial reagent grade and used without further purification. The starting compounds 1,4-dihydroxy-2-naphthoic acid<sup>20</sup> and 3-methyl-2-butenal<sup>16</sup> were prepared by employing previously reported methods. Electrospray ionization (ESI) mass spectrometry (MS) experiments were performed on a LCQ advantage-trap mass spectrometer (Thermo Finnigan, San Jose, CA, USA). Elemental analyses were taken on a Hewlett-Packard Model 185B elemental analyzer.

#### Methyl 1,4-dihydroxy-2-naphthoate (**4a**)

**Method A:** To a prepared ethereal solution of diazo-

methane (*ca.* 15-16 mmol, 25 mL Et<sub>2</sub>O) was added **3** (2.04 g, 10 mmol). The reaction mixture was allowed to stir for 30 min and evaporated under reduced pressure to give the residue. The residue was recrystallized from ethyl acetate to give **4a** (1.88 g, 86%) as pale yellow needles: mp 193-194 °C (lit.<sup>19b</sup> mp 192-193.5 °C); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 11.44 (s, 1H), 9.19 (s, 1H), 8.32 (d, 1H, *J* = 8.1 Hz), 8.18 (d, 1H, *J* = 8.1 Hz), 7.63-7.50 (m, 2H), 7.14 (s, 1H), 3.98 (s, 3H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 170.87, 153.04, 145.48, 129.37, 129.06, 126.75, 125.19, 123.54, 122.52, 105.08, 104.13, 52.90; ESI MS calcd for C<sub>12</sub>H<sub>10</sub>O<sub>4</sub> 219 [M + H]<sup>+</sup>, found 219.

**Method B:** A solution of 30 g (0.15 mol) of **3**, 20.9 g (0.16 mol) ethyldiisopropylamine, and 20.8 mL (0.22 mol) of dimethyl sulfate in 200 mL of dry DMF was stirred at 85 °C for 1 h. The reaction mixture was cooled, poured to aq. NaHCO<sub>3</sub>, and worked up to afford 25.2 g (79%) of **4a**: mp 192-193 °C. The spectral data were identical to those described above in Method A.

**Method C:** To a cooled (0 °C) solution of methyl 1-hydroxy-4-methoxy-2-naphthoate (**4b**) (23.2 g, 0.1 mol) in dry CH<sub>2</sub>Cl<sub>2</sub> (200 mL) was added AlCl<sub>3</sub> (26.2 g, 0.2 mol) and the reaction mixture was stirred for 4 h in a flask fitted with a CaCl<sub>2</sub> tube. The reaction mixture was quenched by the addition of water (200 mL) (exothermic!) and the aqueous solution was further diluted with 1 N HCl (500 mL), extracted with CH<sub>2</sub>Cl<sub>2</sub> (100 mL × 3), dried over MgSO<sub>4</sub> and evaporated *in vacuo*. Flash chromatography on silica gel using EtOAc/petroleum ether (1:19) afforded a yellow powder (21.5 g, 99%), which was recrystallized from methanol to give **4a** as pale yellow needles: mp 193-194 °C. The spectral data were identical to those described above in Method A.

**Methyl 1-hydroxy-4-methoxy-2-naphthoate (**4b**).** To a solution of 1,4-dihydroxy-2-naphthoic acid (20.4 g, 0.1 mol) in CH<sub>3</sub>OH (100 mL) was slowly added H<sub>2</sub>SO<sub>4</sub> (5 mL) at 0 °C and resulting mixture was refluxed for 2 h. Excess CH<sub>3</sub>OH (~70 mL) was distilled off and additional CH<sub>3</sub>OH (50 mL) was added. Resulting mixture was refluxed for 8 h. The white precipitate formed was collected and washed with CH<sub>3</sub>OH, 5% aq. NaOH and water to give **4b** (21.3 g, 92%) as white crystals after recrystallization from CH<sub>3</sub>OH:EtOAc (1:1): mp 136-137 °C (lit.<sup>19b</sup> 137-138 °C). Unreported spectral data are as follows: IR (KBr) ν 1660, 1640, 1605, 1395, 1360, 1255, and 775 cm<sup>-1</sup>. <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 11.59 (s, 1H exchanged with D<sub>2</sub>O), 8.36 (d, 1H, *J* = 8.1 Hz), 8.16 (d, 1H, *J* = 8.1 Hz), 7.60 (td, 1H, *J* = 8.1, 0.8 Hz), 7.53 (td, 1H, *J* = 8.1, 0.8 Hz), 6.95 (s, 1H), 3.95 (s, 3H), 3.92 (s, 3H). <sup>13</sup>C NMR (62.5 MHz, CDCl<sub>3</sub>) δ 171.22, 155.43, 147.49, 129.69, 128.90, 126.30, 125.34, 123.64, 121.77, 104.13, 100.19, 55.52, 52.18; MS (m/e) 232, 200, 129, 102, and 101. Anal. Calcd for C<sub>13</sub>H<sub>12</sub>O<sub>2</sub>: C, 67.23; H, 5.21. Found: C, 67.27; H, 5.22. The resulting reaction mixture was evaporated and dissolved in EtOAc (100 mL) and extracted with 5% NaOH (3 × 50 mL). The combined aq. layers were washed with EtOAc and made acidic (pH = ~1). The resulting solution was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over

MgSO<sub>4</sub> and evaporation of the solvent afforded 4.40 g (2%) of 1-hydroxy-4-methoxy-2-naphthoic acid (**4c**): mp 199-200 °C [lit.<sup>19b</sup> 196-198 °C (dec)]. <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 11.41 (s, 1H exchanged with D<sub>2</sub>O), 8.39 (d, 1H, *J* = 8.1 Hz), 8.16 (d, 1H, *J* = 8.1 Hz), 7.65 (td, 1H, *J* = 8.1, 0.8 Hz), 7.56 (td, 1H, *J* = 8.1, 0.8 Hz), 7.05 (s, 1H), 3.98 (s, 3H).

**6-Hydroxy-2,2-dimethyl-2H-naphtho[1,2-*b*]pyran-5-carboxylic acid (5).** To a mixture of methyl 1,4-dihydroxy-2-naphthoate (**4a**) (20.4 g, 0.1 mol), 3-methyl-2-butenal (8.4 g, 0.1 mol), phenylboronic acid (37.6 g, 0.31 mol), and propionic acid (2 mL) in toluene (200 mL) was refluxed under Dean-Stark trap for 8 h. The reaction mixture was cooled to room temperature and diluted with ether (75 mL). The organic layer was separated, washed with brine (3 × 50 mL), dried, and evaporated *in vacuo*. The resultant residue was purified by column chromatography. The early fractions were recrystallized from pet. ether:EtOAc to afford 24.0 g (89%) of **5** as yellow-green flakes: mp 177-178 °C (lit.<sup>9</sup> mp 177 °C). Unreported spectral data are as follows: IR (KBr)  $\nu$  3400 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz): δ 12.16 (s, 1H, OH), 8.10-8.07 (m, 1H), 7.40-7.36 (m, 2H), 7.16 (d, 1H, *J* = 7.5 Hz, H7), 6.63 (d, 1H, *J* = 10.0 Hz, H4), 5.70 (d, 1H, *J* = 10 Hz, H3), 2.15 (s, 6H, CMe<sub>2</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 62.5 MHz): δ 207.10, 141.78, 130.28, 129.85, 129.02, 128.21, 126.67, 125.55, 125.37, 125.27, 121.78, 118.78, 111.67, 30.95, 27.57. ESI MS: [M+H]<sup>+</sup> at *m/z* 271.

#### Mollugin (1)

**Method A:** To a mixture of methyl 1,4-dihydroxy-naphthoate (**4a**) (21.8 g, 0.1 mol), 3-methyl-2-butenal (8.4 g, 0.1 mol), phenylboronic acid (37.6 g, 0.31 mol), and propionic acid (2 mL) in toluene (200 mL) was refluxed under Dean-Stark trap for 8 h. The reaction mixture was cooled to room temperature and extracted with ether (75 mL). The organic phase was separated, washed with brine (3 × 50 mL), dried, and evaporated *in vacuo*. The resultant residue was purified by column chromatography. The early fractions were recrystallized from methanol to afford mollugin (**1**) as yellow-green flakes (24.5 g, 87%): mp 131-132 °C (lit.<sup>1a</sup> mp 129-130 °C). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz): δ 12.16 (s, 1H, OH), 8.38 (ddd, 1H, *J* = 8.3, 1.4, 0.7 Hz, H7), 8.18 (ddd, 1H, *J* = 8.3, 1.3, 0.7 Hz, H10), 7.62 (ddd, 1H, *J* = 8.3, 6.9, 1.4 Hz, H9), 7.51 (ddd, 1H, *J* = 8.3, 6.9, 1.3 Hz, H8), 7.12 (d, 1H, *J* = 10.1 Hz, H4), 5.68 (d, 1H, *J* = 10.1 Hz, H3), 4.00 (s, 3H, OMe), 1.51 (s, 6H, CMe<sub>2</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 62.5 MHz): δ 172.44, 156.46, 141.57, 129.28, 129.01, 128.81, 126.25, 125.09, 124.01, 122.28, 121.90, 112.54, 102.23, 74.63, 52.21, 26.86 (2 C's). ESI MS: [M+H]<sup>+</sup> at *m/z* 283.

**Method B:** To a solution of 6-hydroxy-2,2-dimethyl-2H-naphtho[1,2-*b*]pyran-5-carboxylic acid (**5**) (27.0 g, 0.1 mol) in CH<sub>3</sub>OH (100 mL) was slowly added H<sub>2</sub>SO<sub>4</sub> (5 mL) at 0 °C and resulting mixture was refluxed for 2 h. Excess CH<sub>3</sub>OH (~70 mL) was distilled off and additional CH<sub>3</sub>OH (50 mL) was added. Resulting mixture was refluxed for 8 h and poured to water. The white precipitate formed was collected and washed with CH<sub>3</sub>OH and water to give **1** (27.8 g, 98%) as yellow flakes after recrystallization from

CH<sub>3</sub>OH:EtOAc (1:1): mp 131-133 °C. The spectral data are identical to those described above.

**Dihydromollugin (2).** A mixture of mollugin (100 mg, 0.35 mmol) and 5% Pd/C (25 mg) in methanol (15 mL) was stirred in a H<sub>2</sub> atmosphere for 5 h. The solution was then filtered through Celite. Evaporation of the solvent gave a yellow solid which was chromatographed on silica gel. The early fractions gave dihydromollugin as a yellow solid (96 mg, 99%): mp 96-97 °C (lit.<sup>1c</sup> mp 96-97 °C). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 12.1 (s, 1H), 8.35 (d, 1H, *J* = 8.1 Hz), 8.16 (d, 1H, *J* = 8.1 Hz), 7.58 (t, 1H, *J* = 7.8 Hz), 7.47 (t, 1H, *J* = 7.8 Hz), 3.97 (s, 3H), 3.04 (t, 2H, *J* = 6.6 Hz), 1.82 (t, 2H, *J* = 6.6 Hz), 1.39 (s, 6H). ESI MS calcd for *m/z* 287 [M+H]<sup>+</sup>.

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