Synthesis of Naturally Occurring Rubilactone, Mollugin, and Dihydromollugin of *Rubia cordifolia*

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Rubilactone (**1**), dihydromollugin (**2**), and mollugin (**3**) are naturally occurring products found in *Rubia cordifolia*, which is a famous Chinese herb with antitumor, viral inhibition and other activities. Synthetic studies were carried out in these naphthoic acid esters starting from 1,4-dihydroxy-2-naphthoic acid. In this study, we finished the synthesis of rubilactone which has not been reported before and also synthesized dihydromollugin and mollugin with better yields with different approaches compared to those previously reported in the literature.

INTRODUCTION

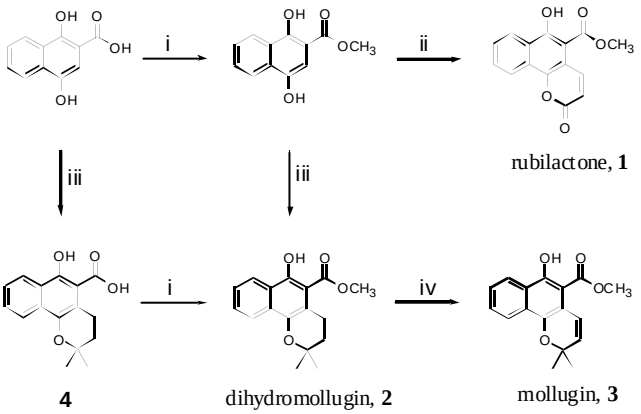
Rubilactone (**1**), dihydromollugin (**2**), and mollugin (**3**) are three naphthoic acid esters components isolated from the roots of *Rubia cordifolia* L. (Rubiaceae),[1-4] a Chinese herbal medicine with antitumor, antiviral and other activities.[3,5] In our previous studies, both **2** and **3** showed strong and **1** showed weak suppressive activity on HBsAg secretion in human hepatoma Hep3B cells.[3] Compound **3** also possessed strong inhibition of arachidonic acid (AA)-induced and collagen-induced platelet aggregation.[6] In an earlier attempt **3** was synthesized from 1,4-dihydroxy-2-naphthoic acid and 3-chloro-3-methyl-1-butyne in 23% overall yield.[7] Compound **2** was obtained by catalytic hydrogenation of **3** over Pd/C[8] or synthesized from methyl 1,4-dihydroxy-2-naphthoate but no yield given.[9] Synthesis of **1** has not been reported yet so far. Herein we would like to report a convenient synthetic method to prepare compounds **1**, **2**, and **3** from 1,4-dihydroxy-2-naphthoic acid.

RESULTS AND DISCUSSION

Compounds **1**, **2**, and **3** were prepared as shown in Scheme I. Upon treatment of methyl 1,4-dihydroxy-2-naphthoate, which was prepared from 1,4-dihydroxy-2-naphthoic acid and CH_2N_2 first, with ethyl propiolate and zinc chloride under reflux, rubilactone (**1**) was obtained in 38% yield as a yellow solid.

1,4-Dihydroxy-2-naphthoic acid was condensed with 2-methyl-3-buten-2-ol in BF_3-etherate to yield the isopentenyl intermediate, while at elevated temperature it gave the intramolecularly cyclized product **4**. Without further purification, esterification of crude product **4** with excess CH_2N_2 produced dihydromollugin (**2**) as a yellow solid in 40% overall yield (based on 1,4-dihydroxy-2-naphthoic acid). Alternatively, a mixture of methyl 1,4-dihydroxy-2-naphthoate, 2-methyl-3-buten-2-ol, and BF_3-etherate in dioxane was refluxed for 4 h to give **2** in 54% yield.[9] Mollugin (**3**) was then easily obtained from **2** in 72% yield by heating with DDQ in dioxane. Methods described here to prepare mollugin (**3**) are more convenient and give better yield than ones in previous reports.

Scheme I[a]



[a](i) CH_2N_2, ether; (ii) ethyl propiolate, $ZnCl_2$, reflux; (iii) 2-methyl-3-buten-2-ol, BF_3-etherate, dioxane, reflux; (iv) DDQ, dioxane, reflux.

In conclusion we reported here the first synthesis of rubilactone (**1**) in only two steps starting from 1,4-dihydroxy-2-naphthoic acid with ethyl propiolate in moderate yield and provided a convenient synthetic method for preparation of dihydromollugin (**2**) and mollugin (**3**).

EXPERIMENTAL SECTION

Melting points were determined with a Yanaco micro-melting point apparatus and are uncorrected. Infrared spectra were obtained on a Nicolet Avatar 320 FTIR spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian Gemini-200 spectrometer. Chemical shifts are reported in parts per million (δ) units relative to internal tetramethylsilane. The mass spectra were measured from a Finnigan GCQ GC/MS spectrometer at 30 eV. Dioxane was distilled from Na/benzophenone and all other solvents were used without further purification. Column chromatography was performed with E. Merck 230-400 mesh silica gel.

Methyl 1,4-dihydroxy-2-naphthoate

To a solution of 1,4-dihydroxy-2-naphthoic acid (3.0 g, 14.7 mmol) in ether (40 mL) was added excess CH_2N_2 at 0 °C for 30 min. Solvent was removed from a rotavapor, and the residue was chromatographed on silica gel eluting with hexane/ethyl acetate (3:1) to yield methyl 1,4-dihydroxy-2-naphthoate (2.7 g, 84%) as a yellow solid: mp 198-199 °C (lit.[10] 172-173 °C); IR (KBr) 1649 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.96 (s, 3H), 7.08 (s, 1H), 7.51-7.68 (m, 2H), 8.09-8.13 (m, 1H), 8.36-8.41 (m, 1H), 11.5 (s, 1H); EIMS *m/z* (rel. int.) 218 (M^+, 97), 204 (85), 186 (100), 158 (21), 130 (32), 102 (71).

Rubilactone (1)

A mixture of methyl 1,4-dihydroxy-2-naphthoate (0.4 g, 1.83 mmol), ethyl propiolate (4 mL), and $ZnCl_2$ (0.35 g) was refluxed for 4 h. After cooling, the precipitates were collected by filtration and recrystallized from chloroform/hexane to yield rubilactone (190 mg, 38%) as a yellow solid: mp 207-208 °C (lit.[4] 216-218 °C); IR (KBr) 1737, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.10 (s, 3H), 6.51 (d, J = 10.2 Hz, 1H), 7.66-7.84 (m, 2H), 8.44-8.52 (m, 2H), 8.78 (d, J = 10.2 Hz, 1H), 11.7 (s, 1H); EIMS *m/z* (rel. int.) 270 (M^+, 45), 256 (30), 238 (100), 210 (45), 182 (25), 126 (19).

Dihydromollugin (2)

A. To a solution of 1,4-dihydroxy-2-naphthoic acid (2.04 g, 10.0 mmol) in dry dioxane (20 mL) was added BF_3-etherate (0.6 mL) and 2-methyl-3-buten-2-ol (1.6 mL, 15.0 mmol). The reaction mixture was stirred at room temperature for 30 minutes and then refluxed for 3 h. After cooling, Et_2O (60 mL) was added and the etheral solution was washed with H_2O, dried over Na_2SO_4, and evaporated to give crude solid which was washed with a small amount of ethyl acetate to yield crude product **4** (1.6 g) as a yellow solid and used in the next step without further purification. ^1H NMR ($CDCl_3$) δ 1.39 (s, 6H), 1.86 (t, J = 6.8 Hz, 2H), 3.18 (t, J = 6.8 Hz, 2H), 7.49-7.68 (m, 2H), 8.13-8.17 (m, 1H), 8.28-8,33 (m, 1H). To a solution of the crude product **4** in ether (40 mL) was added excess CH_2N_2 at 0 °C for 30 minutes. Solvent was removed from a rotavapor, and the residue was chromatographed on silica gel eluting with hexane/ethyl acetate (98:2) to yield dihydromollugin (1.15 g, 40%) as a yellow solid: mp 96-97 °C; IR (KBr) 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (s, 6H), 1.82 (t, J = 6.6 Hz, 2H), 3.04 (t, J = 6.6 Hz, 2H), 3.97 (s, 3H), 7.47 (t, J = 7.8 Hz, 1H), 7.58 (t, J = 7.8 Hz, 1H), 8.16 (d, J = 8.1 Hz, 1H), 8.35 (d, J = 8.1 Hz, 1H), 12.1 (s, 1H); EIMS *m/z* (rel. int.) 286 (M^+, 66), 254 (100), 239 (20), 211 (35).

B. To a solution of methyl 1,4-dihydroxy-2-naphthoate (0.5 g, 2.3 mmol) in dry dioxane (10 mL) was added BF_3-etherate (0.3 mL) and 2-methyl-3-buten-2-ol (0.36 mL, 3.4 mmol). The reaction mixture was refluxed for 4 h. After cooling, Et_2O (50 mL) was added and the etheral solution was washed with H_2O, dried over Na_2SO_4, and evaporated to give a crude yellow product which was chromatographed on silica gel eluting with hexane/ethyl acetate (98:2) to yield dihydromollugin (356 mg, 54%) as a yellow solid.

Mollugin (3)

To a solution of dihydroxymollugin (286 mg, 1.0 mmol) in dry dioxane (15 mL) was added DDQ (272 mg, 1.2 mmol), and the reaction mixture was refluxed over night. After cooling, the precipitates were filtered off and the filtrate was evaporated. The residue was chromatographed on silica gel eluting with hexane/ethyl acetate (98:2) to yield mollugin (205 mg, 72%) as a yellow solid: mp 128-130 °C (lit.[1] 132-134 °C); IR (KBr) 1649 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47 (s, 6H), 4.00 (s, 3H), 5.65 (d, J = 10.2 Hz, 1H), 7.09 (d, J = 10.2 Hz, 1H), 7.46-7.51 (m, 1H), 7.56-7.62 (m, 1H), 8.14-8.17 (m, 1H), 8.33-8.36 (m, 1H), 12.1 (s, 1H); EIMS *m/z* (rel. int.) 284 (M^+, 45), 269 (35), 252 (33), 237 (100).

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Key Words

Rubilactone; Mollugin; Dihydromollugin; *Rubia cordifolia*.

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