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TOTAL SYNTHESIS OF MILTIRONE

Wei Gang Huang,[2] Yun Fei Li,[2]
Wei Lu,[1*] and Haji Akber Aisa[3]

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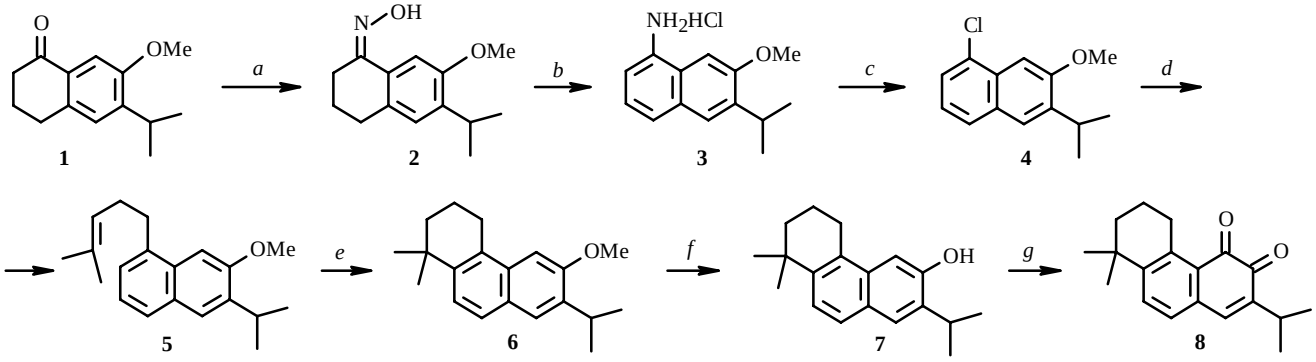
A concise synthesis of miltirone from 6-isopropyl-7-methoxy-1-tetralone is described, in which the naphthol was oxidized with Dess-Martin periodinane to yield miltirone in good yield.

Key words: synthesis, miltirone.

The rhizome of *Salvia miltiorrhiza* Bunge, also known as "Tanshen" or "Danshen", which is an ancient drug in Chinese traditional medicine [1], has been used widely to treat coronary heart disease, menstrual disorders, miscarriage, hypertension, and viral hepatitis [2]. There have been more than 50 ortho- quinone diterpenes, called tanshinones, isolated from Danshen. Many of them exhibit antibacterial [3–5], antidermatophytic [4, 5], antioxidant [6], anti-inflammatory [5, 7], antineoplastic [8], and antiplatelet aggregation [9–11] activities.

In our program of screening the antitumor agent from natural products, miltrone was found to be cytotoxic against a number of cultured tumor cell lines [12]. Miltirone was one of these tanshinones isolated from *S. miltiorrhiza* [13], but also found in other species [6]. In order to modify the structure, we needed to prepare miltirone in large scale. Here we report our synthesis of miltirone from the known starting material 6-isopropyl-7-methoxy-1-tetralone, which was prepared according to the literature [14]. Treatment of **1** with hydroxylamine hydrochloride and 50% NaOH in methanol afforded **2** in excellent yield. The resultant product was transformed to ammonium **3** via a Semmler-Wolff aromatization reaction [15, 16]. By a Sandmeyer reaction, compound **4** was obtained as colorless oil. In the presence of $NiCl_2$(dppp), compound **5** was prepared via a cross-coupling of **4** with the Grinard reagent derived from 1-bromo-4-methylpent-3-ene [17]. Cyclization of **5** and treatment of **6** with boron tribromide at 0°C provided naphthol **7** in high yield. Using Fremy's salt as oxidant agent, compound **7** could be transformed to miltirone (**8**) in high yield. In our strategy, Dess-Martin periodinane was used as the oxidant.



a. $HONH_2HCl$, 50% NaOH, MeOH; *b*. HCl (dry), Ac_2O/HOAc; *c*. (*i*)$NaNO_2$, HCl; (*ii*) CuCl, HCl; *d*. $C_6H_{11}MgBr$, cat. $NiCl_2$(dppp), Et_2O, 97.53%; *e*. $AlCl_3$, CH_2Cl_2, 0°C, 98%; *f*. BBr_3, CH_2Cl_2, 0°C; *g*. Dess-Martin periodinane, CH_2Cl_2, 45% from **6**

1) Department of Chemistry, East China Normal University, 3663 North Zhongshan Road, Shanghai 200062, China, fax 86 21 62602475, e-mail: wlu@chem.ecnu.edu.cn; 2) Shanghai Institute of Materia Medica, SIBS, Chinese Academy of Sciences, Graduate School of Chinese Academy of Sciences, 555, Shanghai 201203, China; 3) Xinjiang Technical Institute of Physics & Chemistry, Chinese Academy of Sciences, 40 South Beijing Road, Urumqi 830011, China. Published in Khimiya Prirodnykh Soedinenii, No. 6, pp. 541-543, November-December, 2006. Original article submitted November 16, 2005.

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In summary, we reported a new synthetic strategy for miltirone in large scale, and demonstrated a facile approach for the construction of the tanshinones.

EXPERIMENTAL

Melting points were taken on a Buchi510 apparatus and were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on either Gemini-300 or Bruker AM-400 instruments. Chemical shifts (δ ppm) were reported for the signal center, and coupling constants J are reported in Hz. High-resolution mass spectra were recorded on Varian MAT-711, MAT-95, or HT-5989 mass spectrometers. Column chromatograph was performed on 200–300 mesh silica gel. All reagents were used directly as obtained commercially, unless otherwise noted.

6-Isopropyl-7-methoxy-1-naphthylamine Hydrochloride (3). Compound **1** (20.6 g, 0.095 mol) and 50% NaOH (6 mL) was refluxed in methanol (80 mL) for 4 h. The resultant mixture was concentrated in vacuo and extracted with dichloromethane. The combined extracts were washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo to yield the crude oxime **2** as a pale yellow solid. The desired product was dissolved in acetic anhydride (17.5 mL) and acetic acid (135 mL) and heated at 100°C for 10 min. Dry hydrogen chloride was then passed through the solution at 100°C for 2 h, when a dark red solution was obtained. The solution was cooled to room temperature and concentrated in vacuo. To the residue was added diethyl ether (175 mL) and the whole stirred vigorously at room temperature. The solid was filtered and washed with diethyl ether to furnish **3** (16.9 g, 52.74%) as a pale green solid.

^{1}H NMR ($CDCl_3$, 300 MHz, J/Hz): 1.28 (d, J = 6.8, 6H), 3.42 (m, 1H), 4.02 (s, 3H), 7.27 (s, 1H), 7.44 (dd, J = 8.0, 7.8, 1H), 7.57 (d, J = 7.7, 1H), 7.93 (s, 1H), 7.97 (d, J = 8.3, 1H).

EIMS (*m/z*): 215 (M^+), 200, 185.

5-Chloro-2-isopropyl-3-methoxynaphthalene (4). Sodium nitrite (2.484 g, 36 mmol) in water (6 mL) was added dropwise to the solution of **3** (9.066 g, 36 mmol) in concentrated hydrochloride (30 mL) and water (30 mL) at 0°C, followed by stirring at 0°C for another 0.5 h. The resultant solution was added to CuCl (9.516 g, 96 mmol) in concentrated hydrochloride (37.5 mL). The reaction was continued at 0°C for 0.5 h and at 75°C for 2 h. The resultant mixture was diluted with water and extracted with ether. The combined extract was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatograph (petroleum) to afford **4** (3.381 g, 40%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz, J/Hz): 1.35 (d, J = 6.8, 6H), 3.48 (m, 1H), 4.04 (s, 3H), 7.25 (dd, J = 8.0, 7.4, 1H), 7.50 (s, 1H), 7.52 (d, J = 7.4, 1H), 7.56 (s, 1H), 7.70 (d, J = 7.9, 1H).

EIMS (*m/z*): 236 $(M+2)^+$, 234 (M^+), 219, 204.

2-Isopropyl-3-methoxy-5-(4-methyl-pent-3-enyl)-naphthalene (5). To a mixture of $C_6H_{11}MgBr$ (57.3 mmol in 30 mL dry ether) and $NiCl_2$(dppp) (205 mg, 0.43 mmol) was added a solution of **4** (3.032 g, 12.918 mmol) in Et_2O (30 mL), and the resultant mixture was stirred under an atmosphere of nitrogen overnight. The mixture was poured into ice water and extracted with ethyl acetate. The organic extract was washed with 1N HCl and brine, dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified by flash chromatograph (petroleum–ethyl acetate 100: 1) to furnish **5** (3.558g, 97.53%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz, J/Hz): 1.35 (d, J = 7.0, 6H), 1.65 (s, 3H), 1.76 (s, 3H), 2.48 (m, 2H), 3.06 (m, 2H), 3.48 (m, 1H), 4.00 (s, 3H), 5.35 (t, J = 7.0, 1H), 7.30 (m, 3H), 7.65 (m, 2H).

EIMS (*m/z*): 282 (M^+), 267, 213.

1,2,3,4-Tetrahydro-1,1-dimethyl-6-methoxy-7-isopropyl-phenanthrene (6). A solution of **5** (1.779 g, 6.299 mmol) in CH_2Cl_2 (50 mL) was cooled to 0°C. $AlCl_3$ (1.815 g, 13.592 mmol) was added in one portion. The solution was stirred at 0°C for 30 min and then poured into ice water. The aqueous phase was separated and extracted with diethyl ether. The combined organic phase was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. Column chromatograph (petroleum–ethyl acetate 100: 1) yielded **6** (1.779 g, 100%) as a pale yellow solid.

^{1}H NMR ($CDCl_3$, 300 MHz, J/Hz): 1.28 (d, J = 6.8, 6H), 1.36 (s, 6H), 1.72 (m, 2H), 1.96 (m, 2H), 3.05 (t, J = 6.4, 2H), 3.42 (m, 1H), 3.95 (s, 3H), 7.18 (s, 1H), 7.36 (d, J = 9.1, 1H), 7.56 (s, 1H), 7.98 (d, J = 9.0, 1H).

EIMS (*m/z*): 282 (M^+), 267, 2225, 200, 185.

Miltirone (8). To the ice cooled solution of **6** (1.779 g, 6.299 mmol) in dichloromethane (50 mL) was added dropwise boron tribromide (3.0 mL, 31.495 mmol). The reaction mixture was stirred at room temperature for 2 h and then poured into ice water. The aqueous phase was separated and extracted with dichloromethane. The combined organic phase was washed with

water and brine, dried over $MgSO_4$, and concentrated in vacuo. Without further purification the phenol **7** was dissolved in dichloromethane (100 mL) and Dess-Martin periodinane (2.827 g, 6.93 mmol) was added. The solution was stirred at room temperature overnight and then diluted with diethyl ether. The organic phase was separated and washed with 1 N NaOH, water, and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by column chromatograph (petroleum–ethyl acetate 100: 1) and recrystallized from hexane to give miltirone (**8**) (0.800 g, 45% from **10**) as red crystals. Mp: 98–100°C (mp: 100°C [13]).

^{1}H NMR ($CDCl_3$, 300 MHz, J/Hz): 1.14 (d, J = 6.8, 6H), 1.26 (s, 6H), 1.64 (m, 2H), 1.78 (m, 2H), 3.00 (m, 1H), 3.16 (t, J = 6.6, 2H), 7.05 (s, 1H), 7.10 (d, J = 7.8, 1H), 7.58 (d, J = 7.9 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.8, 21.4, 26.8, 19.8, 31.7, 34.4, 37.8, 127.8, 128.2, 133.7, 134.4, 139.8, 144.4, 144.9, 149.5, 181.6, 182.4.

EIMS (*m/z*): 284 $(M+2)^+$.

HRMS calcd. for $C_{19}H_{22}O_2$ 282.1620, Found 282.1617.

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