A short and efficient synthesis of cytotoxic 3-isopropylnaphthalene-1,2-dione *via* 3-hydroxy-2-naphthoic acid

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This paper is dedicated to Professor Udo H. Brinker on the occasion of his 65th birthday

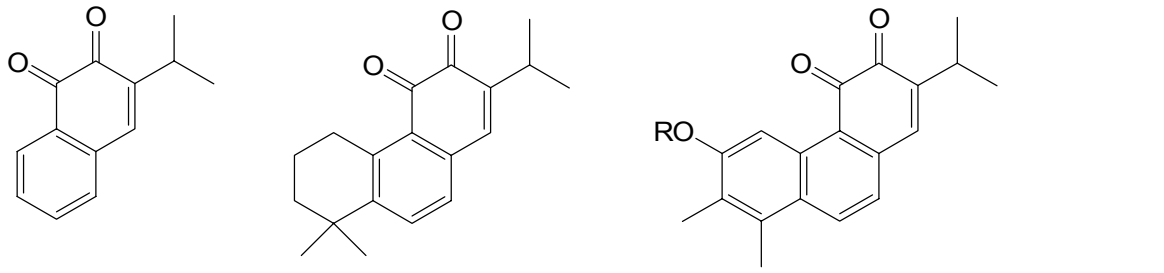
Abstract

3-Isopropylnaphthalene-1,2-dione (**1**) was synthesized from 3-hydroxy-2-naphthoic acid (**5**) in 4 steps (59% overall yield). After conversion of **5** to its methyl ester derivative, the crucial steps of the synthesis were the treatment of the ester with 4 eq MeMgI and then Pd-C catalyzed hydrogenation to give 3-isopropylnaphthalen-2-ol (**8**). Oxidation of **8** with *m*-chloroperbenzoic acid gave **1** in good yield.

Keywords: 3-Isopropylnaphthalene-1,2-dione, 3-Hydroxy-2-naphthoic acid, MeMgI, hydrogenation, oxidation

Introduction

3-Isopropylnaphthalene-1,2-dione (**1**) is found as a structural moiety in many natural products. For example, miltirone (**2**)[1] is a cytotoxic natural product and contains the 3-isopropylnaphtelene-1,2-dione moiety. Ulubelen et al.[2] reported that multiorthoquinone (**3**) and 2-demethylmultiorthoquinone (**4**), quinoid natural products, show very efficient anti-tuberculosis activity. Huang et al.[3] reported **1** itself and its derivatives to have remarkable cytotoxic activities against A549 and HCT-116 cell lines and to have inhibitory activity on Cdc25 phosphatases, key regulators of the cycle during normal eukaryotic cell division and mediators of the checkpoint response in cells with DNA damage.



1 **2** Miltirone **3** R=Me; Multiorthoquinone

4 R=H; 2-Demethylmultiorthoquinone

Figure

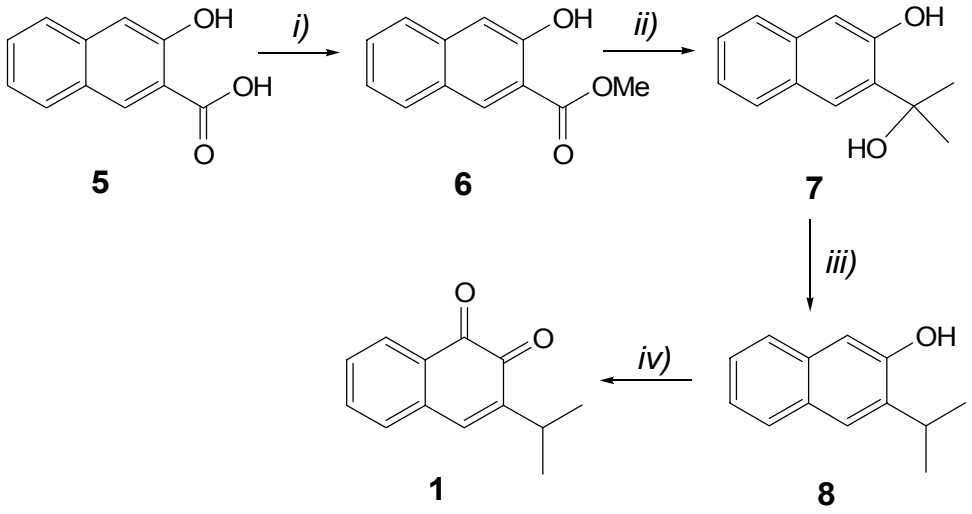
To date, there have been two reports on the synthesis of **1**. The first synthesis of **1**, based on Clemmensen reduction of 2-hydroxy-3-isopropyl-1,4-naphtoquinone, was performed by Fieser and Bader.[4] However, the 2-hydroxy-3-isopropyl-1,4-naphtoquinone is prepared by reduction of lapachol, followed by two step Hooker oxidation, and the overall yield is <12%.[5] The second synthesis of **1** was performed by Chang et al.,[6] starting from 2-isopropylanisol in 9 steps and in ~ 7% overall yield. In this paper we describe a novel, concise, short, and very efficient synthesis of **1** starting from 3-hydroxy-2-naphthoic acid, a very cheap commercially available compound.

Results and Discussion

Our synthesis was based on a transformation of the carboxyl group of **5** to an isopropyl group to give 3-isopropylnaphthalen-2-ol (**8**) and then its oxidation to give **1**. For this, first 3-hydroxy-2-naphthoic acid (**5**) was converted to the corresponding methyl ester **6** by refluxing in MeOH in the presence of p-TsOH in a yield of 92%. Lammer[7] reported the direct preparation of carbinol **7** from ester **6** by treatment with an excess of MeMgI. Following this procedure, ester **6** was reacted with 4 equivalents of MeMgI to give carbinol **7** in excellent yield (89%). Pd-C catalyzed hydrogenation of **7** gave 3-isopropylnaphthalen-2-ol (**8)** in 97% yield. Alternative methods have been used to oxidize naphthol **8** to naphthalene-1,2-dione **1**. Chang et al.[6] used Fremy's salt, $(KSO_3)_2NO$, for this purpose. Huang et al.[3] oxidized naphthol **8** to naphthalene-1,2-dione **1** by reaction with Dess-Martin periodinane. Ghera and Ben-David[8] reported the conversion of 3-alkyl-2-naphthols to 3-alkyl-1,2-naphthalenediones based on oxidation with m-chloroperbenzoic acid. The application of this method to 3-isopropylnaphthalen-2-ol gave 3-isopropylnaphthalene-1,2-dione (**1**) in a yield of 74% (Scheme 1).

Conclusions

In summary, starting from 3-hydroxy-2-naphthoic acid, a very cheap commercially available compound, we developed an alternative and efficient method for the preparation of 3-isopropylnaphthalene-1,2-dione (**1**), a potent antitumor compound, in only 4 steps and in 59% overall yield. Further, the intermediary 3-isopropylnaphthalen-2-ol (**8**) should be a useful synthon for the preparation of biologically active naphthalene compounds.



Scheme 1. (i) MeOH, p-TsOH, reflux, 24 h, 92%; (ii) MeMgI (4 eq); THF; 12 h; 89%; (iii) H_2, Pd-C, MeOH, 3 h, 97%; (iv) *m*-chloroperbenzoic acid (3 eq), CH_2Cl_2, 2 h, 74%.

Experimental Section

General Procedures. Column chromatography (CC): silica gel 60 (70–230 mesh). TLC: Silica gel 60 F_{254} plates (Merck). Solvents were purified and dried by standard procedures before use. M.p.: Büchi-539 cap. melting-point apparatus; uncorrected. ^{1}H- and ^{13}C-NMR Spectra: at 200 or 50 MHz, on Varian spectrometer; δ in ppm, *J* in Hz. EI-MS: Thermo-Finnigan mass analyzer; in *m/z* (rel. int. in %). Elemental analyses were carried out with a Leco CHNS-932 instrument.

Methyl 3-hydroxy-2-naphthoate (6). To a solution of 3-hydroxy-2-naphthoic acid (**5**) (5.00 g, 26.6 mmol) in dry MeOH (150 mL) was added 50 mg of p-TsOH. The resulting mixture was refluxed for 24 h. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc (100 mL) and washed with saturated $NaHCO_3$ (10 mL), brine (10 mL), and water (10 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure to give ester **6** as a yellow solid (4.95 g, 92%). M.p. 71-73° (solidified). (lit[9] m.p. 73-74°). R_f=0.88 (1:1 EtOAc/Hexane). ^{1}H-NMR (200 MHz, $CDCl_3$): 10.42 (br. *s*, OH); 8.49 (*s*, 1H, H-

C(1)); 7.80 (br.*d*, 1H, H-C(5) or H-C(8), *J*=8.3 Hz); 7.69 (br. *d*, 1H, H-C(5) or H-C(8), *J*=8.3 Hz); 7.50 (br. *t*, 1H, H-C(6) or H-C(7), *J*=7.9 Hz); 7.32 (*s*, 1H, H-C(4)); 7.32 (br. *t*, 1H, H-C(6) or H-C(7), *J*=7.5 Hz); 4.03 (*s*, 3H, OCH_3). ^{13}C-NMR (50 MHz, $CDCl_3$): 170.3 (COOMe); 156.4 (C(3)); 138.0; 132.5; 129.3; 129.2; 127.2; 126.4; 124.0 ; 114.3; 111.8; 52.6 (OCH_3). EI-MS: 202.5 (M^+, 40); 170.1 (100); 142.3 (86); 71.3 (18).

3-(2-Hydroxypropan-2-yl)naphthalen-2-ol (7). A solution of ester **6** (3.03 g; 15.0 mmol) in THF (50 mL) was cooled to 0 °C and a solution of MeMgI in ether (3M, 20 mL; 60 mmol) was added dropwise under Ar atm. at the same temp. The resulting mixture was stirred for 12 h at r.t. The mixture was cooled to 0 °C and saturated NH_4Cl solution (20 mL) added. The organic layer was extracted with EtOAc (3 x 35 mL). The solution was dried ($MgSO_4$) and the solvents was evaporated to give carbinol **7** as a crude product. Chromatography of the crude **7** on a silica gel column (90 g) eluting with EtOAc/hexane (1:4) gave pure **7** as a light yellow solid (2.69 g; 89%). M.p. 133-135° (solidified). (lit[7] m.p. 140-141°). R_f=0.41 (1:4 EtOAc/Hexane). ^{1}H-NMR (200 MHz, $CDCl_3$): 9.07 (s, 1H, ArOH); 7.70 (br. *d*, 1H; H-C(5) or H-C(8), *J*=8.8 Hz); 7.63 (br. *d*, 1H, H-C(5) or H-C(8); *J*=8.1 Hz); 7.56 (*s*, 1H; H-C(4); 7.40 (*dt*, 1H; H-C(6) or H-C(7), *J*=7.5 Hz, *J*=1.4 Hz); 7.30 (*dt*, 1H; H-C(6) or H-C(7), *J*=8.1 Hz, *J*=1.4 Hz); 7.21 (*s*, 1H, H-C(1)); 2.87 (*s*, 1H, OH); 1.76 (*s*, 6H, 2xCH_3). ^{13}C-NMR (50 MHz, $CDCl_3$): 153.7 (C(2)); 134.2; 133.5; 128.1; 127.7; 126.2; 125.9; 124.5; 123.4; 111.8; 75.7 (C(OH)Me_2); 30.1 (2xCH_3). EI-MS: 184.4 (M^+-H_2O, 100); 169.3 (23); 155.3 (22); 141.3 (91); 128.3 (15); 115.2 (32). Anal. calcd for $C_{13}H_{14}O_2$ (202.10): C, 77.20; H, 6.98; Found: C, 77.37; H, 7.02.

3-Isopropylnaphthalen-2-ol (8). To a solution of carbinol **7** (2.00 g; 9.89 mmol) in MeOH (150 mL) was added 10% Pd-C (200 mg). The mixture was stirred under H_2 (1 atm) for 3 h at r.t. The filtration of Pd-C and then evaporation of the solvent gave **8** as a reddish solid (1.78 g; 97%). M.p. 96-98° (solidified). (lit[5] m.p. 92-93°). R_f=0.53 (1:4 EtOAc/Hexane). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.75 (br. *d*, 1H, H-C(5) or H-C(8), *J*=7.9 Hz); 7.65 (br. *s*, 1H, H-C(4)); 7.63 (br. *d*, 1H, H-C(5) or H-C(8), *J*=7.5 Hz); 7.38 (*dt*, 1H, H-C(6) or H-C(7), *J*=6.8 Hz; *J*=1.6 Hz); 7.34 (*dt*, 1H, H-C(6) or H-C(7), *J*=7.8 Hz, *J*=1.9 Hz); 7.08 (*s*, 1H, H-C(1)); 3.36 (*septet*, 1H; CHMe_2, *J*=6.8 Hz); 1.36 (*d*, 6H, 2xCH_3, *J*=6.8 Hz). ^{13}C-NMR (50 MHz, $CDCl_3$) δ 152.1 (C(2)); 137.1; 132.9; 129.2; 127.4; 125.6; 125.5; 125.1; 123.4; 109.4; 27.5 (CHMe_2); 22.6 (2xCH_3). EI-MS: 186.4 (M^+, 53); 171.3 (100); 152.3 (32); 141.3 (16); 128.3 (16); 115.2 (17).

3-Isopropylnaphthalene-1,2-dione (1). To a solution of **8** (0.98 g; 5.26 mmol) in CH_2Cl_2 (20 mL) was added m-chloroperbenzoic acid (3.54 g, 77%, 15.8 mmol) over 30 min at r.t. The reaction mixture was stirred for an additional 2 h and then poured into water (50 mL). The organic phase was extracted with CH_2Cl_2 (2x25 mL), washed with 5% $NaHCO_3$ (50 mL) and brine (50 mL), and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave 3-isopropylnaphthalene-1,2-dione (**1**) as a yellow solid (0.78 g; 74%). M.p. 129-131° (from CH_2Cl_2-hexane). (lit[6] m.p. 126-128°). R_f=0.42 (1:4 EtOAc/Hexane). ^{1}H-NMR (200 MHz, $CDCl_3$): 8.00 (*d*, 1H, H-C(5) or H-C(8), *J*=7.4 Hz); 7.60 (*t*, 1H, H-C(6) or H-C(7), *J*=7.6 Hz); 7.39 (*t*, 1H, H-C(6) or H-C(7), *J*=8.6 Hz); 7.28 (*d*, 1H, H-C(5) or H-C(8), *J*=8.4 Hz); 7.13 (*s*, 1H, H-C(4)); 3.04 (*septet*, 1H; CHMe_2, *J*=6.9 Hz); 1.16 (*d*, 6H, 2xCH_3, *J*=6.9 Hz). ^{13}C-NMR

(50 MHz, $CDCl_3$): 180.8 (C(1) or C(2)); 179.6 (C(1) or C(2)); 146.4; 138.4; 135.8; 135.5; 130.5; 129.8; 129.7; 129.3; 27.1 ($\underline{C}HMe_2$); 21.5 ($2x\underline{C}H_3$). ^{1}H-NMR is in good agreement with data given in the literature.[6]

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