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A Convenient Synthesis of Monpain Trimethylether.

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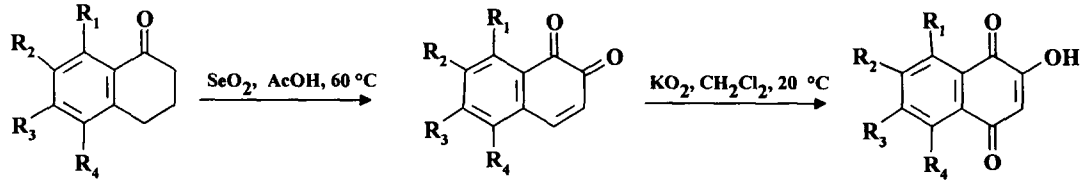
Abstract : A high yield synthesis of various 2-hydroxy-1,4-naphtoquinones was achieved by SeO_2 oxidation of 1-tetralones into the corresponding 1,2-quinones, followed by heterogeneous phase KO_2 mediated oxidation. Application of this synthesis to 5,7,8-trimethoxy-1-tetralone gave 2-hydroxy-5,7,8-trimethoxy-1,4-naphtoquinone **3d** or monpain trimethylether. © 1997 Elsevier Science Ltd.

2-Hydroxy-1,4-naphtoquinones have been described as occuring in natural pigments (for example : spinochromes in sea urchins[1]) or involved in the synthesis of oxygenated heterocycles[2]. Various syntheses of naphtoquinones have been used depending on the substitution pattern : hydroquinone-maleic anhydride condensation for hydroxy or halogeno derivatives[1]; tetralone route for methoxy or hydroxyquinones[3,4,5,6] and potassium superoxide mediated oxidation of dinaphtols[7].

However, the previous methods were not convenient for the synthesis of a highly polymethoxylated structure such as the monpain trimethylether **3d**, obtained from *Helicobasidium monpa* Tanaka[8], which proved to be a suitable intermediate in our synthesis of bikaverin[2]. Baillie and Thomson[9] first obtained this compound in a poor yield (13%) by reaction of N,N-dimethyl-4-nitrosoaniline with 5,7,8-trimethoxy-1-tetralone **1d**. Subsequent acidic hydrolysis of the dianilide gave the 2-hydroxy-5,7,8-trimethoxy-1,4-naphtoquinone **3d.**

In this paper, we report a high yield and clean synthesis converting different monomethoxylated 1-tetralones **1a-c** and 5,7,8-trimethoxylated 1-tetralone **1d** into the corresponding 2-hydroxy-1,4-naphtoquinones **3a-d** in two steps.

The first step utilized SeO_2 regiospecific oxidation[10]of the 1-tetralones **1a-d** into the corresponding 1,2-naphtoquinones **2a-d** (without formation of the 1,4-isomers) (Scheme 1). Subsequent heterogeneous oxidation with potassium superoxide in dichloromethane provided in very good yields the 2-hydroxy-1,4-naphtoquinones **3a-d** (Table 1).



1 **2** **3**

Scheme 1

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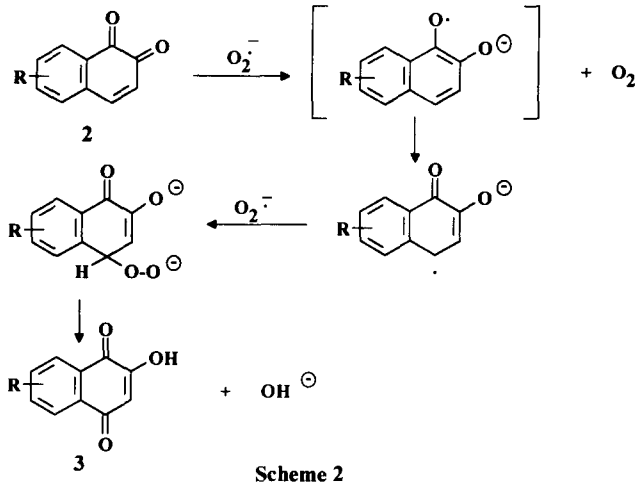

Scheme 2

A mechanism[5] of the KO_2 oxydation *via* anion radical is postulated in the scheme 2. The reaction of superoxide anion with 1,2-quinone **2** first produces a semi-quinone radical anion intermediate, that reacts with a second molecule of superoxide anion into an hydroperoxydianion ; subsequent loss of OH^- gives 2-hydroxy-1,4-naphtoquinones **3**.

Table 1 : 1,2- and 1,4-naphtoquinones

1		2		3	
1a	$R_1 = R_2 = R_3 = H$, $R_4 = OCH_3$	**2a**	Y= 78%	**3a**	Y = 95%
1b	$R_1 = R_2 = H$, $R_3 = OCH_3$, $R_4 = H$	**2b**	Y= 72%	**3b**	Y = 95%
1c	$R_1 = H$, $R_2 = OCH_3$, $R_3 = R_4 = H$	**2c**	Y= 60%	**3c**	Y = 97%
1d	$R_1 = R_2 = R_3 = OCH_3$, $R_4 = H$	**2d**	Y= 60%	**3d**	Y = 98%

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(11) *General procedure*: examples **2d** and **3d**: To a solution of **1d** (10 mmol) in 30 mL of acetic acid was added finely powdered SeO_2 (2.22 g, 20 mmol) was added. The mixture was warmed at 60 °C for 4 h under nitrogen atmosphere. After filtration over Celite and solvent removal, crystallization of the residue from ethyl acetate yielded **2d.** To a solution of **2d** (0.248 g, 1 mmol) in 20 mL of dry CH_2Cl_2 under nitrogen atmosphere, finely powdered KO_2 (0.14 g, 2 mmol, provided by VENTRON) was added. After 15 min stirring, careful hydrolysis by acidification (HCl 4M) followed by CH_2Cl_2 extraction provided **3d** (yield = 98%).

2d : purple crystals; m.p. : 115 °C; IR (KBr) : 1640 cm^{-1}; UV (ethanol) : 482 nm (ε = 4000); ^{1}H-NMR (200 MHz, $CDCl_3$) : δ 4.00 (s, 3H, 7-OCH_3), 4.05 (s, 3H, 5-OCH_3), 4.10 (s, 3H, 8-OCH_3), 6.30 (d, J= 12 Hz, 1H, H_3), 6.68 (s, 1H, H_6), 7.90 (d, J= 12 Hz, 1H, OH); ^{13}C-NMR (75 MHz, $CDCl_3$) : δ 56.3, 56.4, 61.2, 102.1, 115, 123.2, 125.4, 140.2, 148.0,154.03, 157.1,179.2, 181.1; MS : 250 (M^+ + 2 ; 6%), 248 (M^+ ; 2%), 223 (8%), 220 (4%). **3d**: orange needles (ethanol); m.p. : 175 °C; IR (KBr) : 3305, 1650 cm^{-1}; UV (ethanol) : 292 nm (ε = 3080); ^{1}H-NMR (200 MHz, $CDCl_3$) : δ 3.80 (s, 1H, 7-OCH_3), 3.95 (s, 6H, 5-OCH_3, 8-OCH_3), 6.20 (s, 1H, H_3), 6.80 (s, 1H, H_3), 7.30 (s, 1H, OH); ^{13}C-NMR (75 MHz, $CDCl_3$) : δ 56.1, 56.5, 60.5, 103.3, 111,4, 122.9, 144.1, 154.2, 157.1, 158.1, 180.6, 183.0; MS: 260 (M^+ ; 100%), 249 (40%).

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