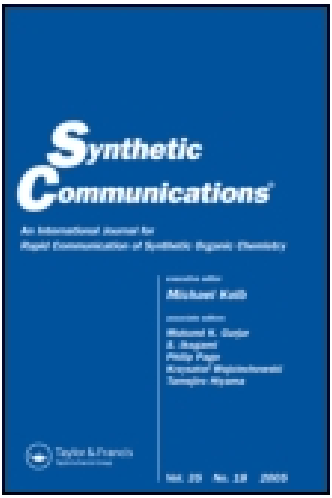

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Efficient Synthesis of Biologically Interesting Dehydro-α-Lapachone and α-Lapachone

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ABSTRACT

An efficient synthesis of biologically active dehydro-α-lapachone and α-lapachone has been carried out starting from 2-hydroxy-1,4-naphthoquinone by a tandem Knoevenagel-electrocyclic reaction.

Key Words: Dehydro-α-lapachone; α-Lapachone; 2-Hydroxy-1,4-naphthoquinone; Knoevenagel-electrocyclic reaction.

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Lapachone and dehydrolapachone derivatives (**1**–**6**) are widely distributed in nature (Fig. 1). They are primarily isolated from the Central and South American lapacho tree (*Tabebuia avellanedae*) as 1,2- and 1,4-naphthoquinone moieties.[1] They are also isolated from *Catalpa ovata*, which is found in Japan and China.[2] They all have antibacterial, antifungal, antitrypanosomal, antimalarial, and antitumor properties and are used in traditional medicines for the treatment of pyrexia, jaundice, and edema by nephritis in Japan and China.[3] Biological properties also include reduction of HIV-1 replication, suppression of both acute and chronic infections, inhibition of DNA topoisomerase I, induction of chromosomal alterations, inhibition of reverse transcriptase and DNA polymerase-α, and blocking of activation of NF-*k*B and AP-1.[4–10] They also have potential clinical utility in the treatment of human leukemia and prostate cancer.[11,12] In particular, a combination of β-lapachone and toxol is combined synergistically to induce cell death in so many types of human carcinoma cells such as ovarian, breast prostate, lung, melanoma, colon, and pancreatic cells.[13] Several synthetic approaches of lapachone and dehydrolapachone have been reported.[14] The common protocol for the synthesis of α- lapachone (**1**) and β-lapachone (**2**) was made by the acid-catalyzed cyclization of lapachol (**8**), which was synthesized from 2-hydroxy-1,4-naphthoquinone (**7**) as shown in Sch. 1.[14a] However, this synthetic exploitation has been limited due to many reaction steps, strong reaction conditions, and side reactions involving O-alkylation product **9**. The necessity for overcoming these serious problems has prompted research for improved synthetic methods of the products. We have been interested in $Yb(OTf)_3$- or $InCl_3$-catalyzed

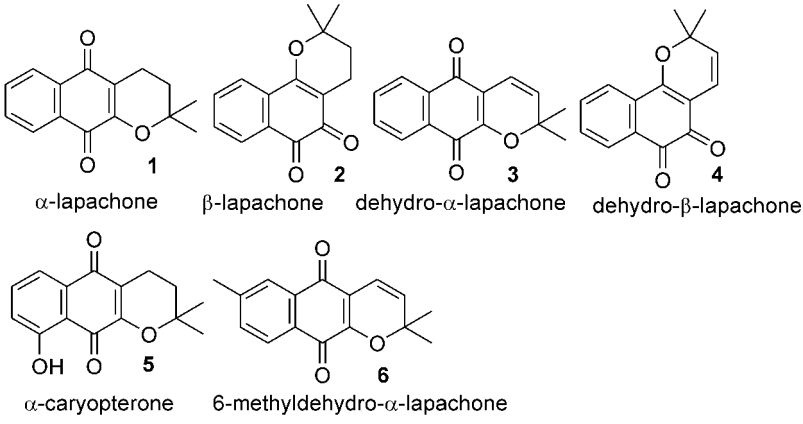
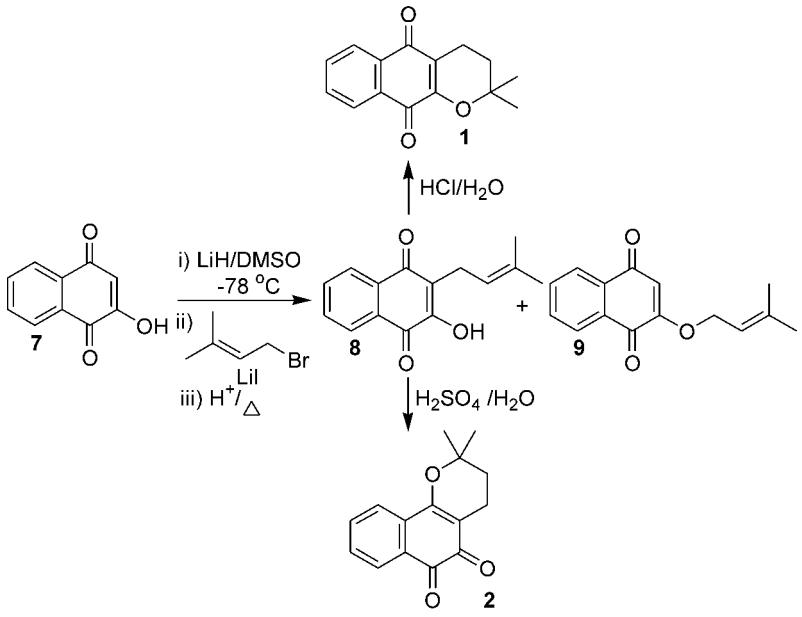


Figure 1.

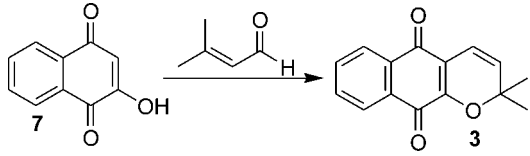


Scheme 1.

reactions of 1,3-dicarbonyls with enals because of the power they offer in the synthesis of 2*H*-pyrans.[15] The method we have developed for the synthesis of 2*H*-pyrans seemed ideal for the synthesis of lapachone derivatives. We report here a simple and efficient method for the synthesis of dehydro-α-lapachone and α-lapachone starting from 2-hydroxy-1,4-naphthoquinone (**7**).

Reaction of **7** with 3-methyl-2-butenal was first examined utilizing several catalysts (Table 1). Both indium (III) chloride (10 mmol%) and ytterbium (III) triflate (10 mol%) catalysts in acetonitrile afford a small fraction of dehydro-α-lapachone (**3**) in 5% and 10% yields, respectively. We also surveyed other solvents to increase a yield in the presence of $Yb(OTf)_3$. The higher yield was obtained in DMF (55%) at 100°C for 5 h. In order to find the optimized reaction conditions, other reagents also were investigated. With pyridine as a catalyst and a solvent, dehydro-α-lapachone (**3**) was formed in 54% yield. The best yield (75%) was obtained with ethylenediamine diacetate (10 mol%) in MeOH. Interestingly, in these reactions, dehydro-α-lapachone (**3**) was obtained as a sole product. The spectroscopic properties of synthetic material **3** agreed well with those reported in the literature.[1a] Related work concerning the formation of **3** in the presence of triethylamine was reported by Tapia et al. in low yield.[16]

Table 1. Effect of catalysts and solvents in the reaction of **7** and 3-methyl-2-butenal.



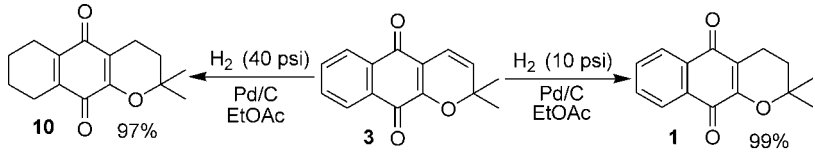
Catalyst	Condition	Yield (%)
$lnCl_3$ (10 mol %)	acetonitrile, reflux, 5 h	5
$Yb(OTf)_3$ (10 mol %)	acetonitrile, reflux, 5 h	10
$Yb(OTf)_3$ (10 mol %)	MeOH, rt, 10 h	31
$Yb(OTf)_3$ (10 mol %)	DMF, 100°C, 5 h	55
Pyridine (excess)	$MgS0_4$, reflux, 5 h	54
Ethylenediamine diacetate	MeOH, rt, 5 h	75

The conversion of dehydro-α-lapachone (**3**) to α-lapachone (**1**) was treated with hydrogen (Sch. 2). Hydrogenation of dehydro-α-lapachone (**3**) in the presence of 10% Pd/C at 40 psi for 1 h gives reduced adduct **10** in 97% yield, whereas reaction at 10 psi for 20 min yields α-lapachone (**1**) in 99% yield.[17] Spectroscopic data of our synthetic material **1** is the same as values published in the literature for the natural product,[1a] and by direct comparison with ^{1}H NMR and IR.[1d–e]

In conclusion, a new, efficient synthetic route to the biologically active dehydro-α-lapachone (**3**) and α-lapachone (**1**) has been developed from the readily available 2-hydroxy-1,4-napthoquinone (**7**) by a tandem-Knoevenagel-electrocyclic reaction.[18]

EXPERIMENTAL

All experiments were carried out under a nitrogen atmosphere. Merck precoated silica gel plates (Art. 5554) with fluorescent indicator were used



Scheme 2.

for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). Melting points were determined in capillary tubes on a Fisher-Johns apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker Model ARX (300 MHz) spectrometer. IR spectra were recorded on a Jasco FTIR 5300 spectrophotometer. HRMS mass spectra were carried out by Korea Basic Science Institute (Daegu).

Dehydro-α-lapachone (3). Method A: the 2-hydroxy-1,4-naphthoquinone (**7**) (174 mg, 1 mmol) and 3-methyl-2-butenal (168 mg, 2 mmol) were dissolved in DMF (5 mL), and $Yb(OTf)_3$ (62 mg, 1 mmol) was added at room temperature. The mixture was stirred at 100°C for 5 h and then cooled to room temperature. Removal of solvent at reduced pressure left an oily residue, which was then purified by column chromatography on silica gel to give **3** (132 mg, 55%) as a solid: mp 145–146°C (lit. 148°C[1e]); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11–8.05 (2H, m), 7.70–7.64 (2H, m), 6.64 (1H, d, $J = 10.0$ Hz), 5.71 (1H, d, $J = 10.0$ Hz), 1.54 (6H, s); IR (KBr) 3079, 3017, 2976, 2922, 1676, 1647, 1593, 1570, 1416, 1331, 1275, 1211, 1190, 1134, 968, 947 cm^{-1}.

Method B: the 2-hydroxy-1,4-naphthoquinone (**7**) (1.740 g, 10 mmol) and 3-methyl-2-butenal (1.680 mg, 20 mmol) were dissolved in MeOH (40 mL), and ethylenediamine diacetate (180 mg, 1 mmol) was added at room temperature. The mixture was stirred at room temperature for 5 h. Removal of solvent at reduced pressure left an oily residue, which was then purified by column chromatography on silica gel to give **3** (1.802 g, 75%) as a solid.

2,2-Dimethyl-3,4,6,7,8,9-hexahydro-2*H*-benzo[*g*]chromene-5,10-dione (10). To synthetic material **3** (200 mg, 0.84 mmol) in a Parr bottle in EtOAc (10 mL) was added 10% Pd/C (20 mg). The bottle was shaken for 1 h at 40 psi H_2. Removal of solvent at reduced pressure left an oily residue, which was then purified by column chromatography on silica gel to give **10** (198 mg, 97%) as a solid: mp 153–155°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44–2.35 (6H, m), 1.70 (2H, t, $J = 6.6$ Hz), 1.67–1.63 (4H, m), 1.35 (6H, s); IR (KBr) 2943, 1667, 1649, 1630, 1609, 1456, 1397, 1362, 1298, 1275, 1221, 1159, 1117, 936 cm^{-1}; HRMS m/z (M^+) Calcd. for $C_{15}H_{18}O_3$, 246.1256. Found 246.1258.

α-Lapachone (1). To synthetic material **3** (300 mg, 1.25 mmol) in a Parr bottle in EtOAc (10 mL) was added 10% Pd/C (20 mg). The bottle was shaken for 20 min at 10 psi H_2. Removal of solvent at reduced pressure left an oily residue, which was then purified by column chromatography on silica gel to give **1** (299 mg, 99%) as a solid: mp 113–114°C (lit. 116°C,[1e]); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08–8.02 (2H, m), 7.70–7.62 (2H, m), 2.60 (2H, t, $J = 6.6$ Hz), 1.80 (2H, t, $J = 6.6$ Hz), 1.42 (6H, s); IR (KBr) 2974, 2948, 1682, 1638, 1613, 1578, 1391, 1341, 1310, 1273, 1208, 1119, 961 cm^{-1}.

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