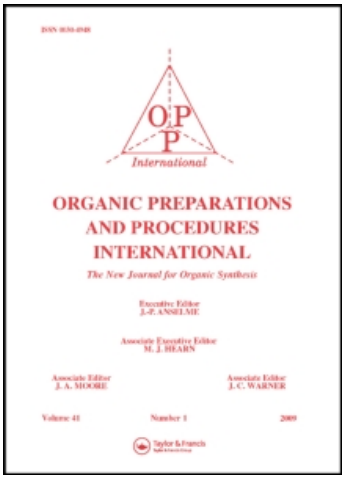

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An Improved One-pot Procedure for the Preparation of β-Lapachone and *nor*-β-Lapachone, Two Potent Drug Prototypes

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An Improved One-pot Procedure for the Preparation of β-Lapachone and *nor*-β-Lapachone, Two Potent Drug Prototypes

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Since the finding that lapachol (**1**), a natural 1,4-naphthoquinone isolated from the *Lapacho* trees, displays antitumor activity against carcinoma Walker 256, many other natural and synthetic 1,2- and 1,4-naphthoquinones have been reported as potent antitumor compounds.[1] Among the natural cytotoxic 1,2-naphthoquinones, β-lapachone (**2**) or ARQ501 is one of the most studied quinones in recent years. It is a natural pyran-*ortho*-naphthoquinone originally obtained from heartwood of several *Lapacho* trees that belong to the genus *Tabebuia* (*Bigoniaceae*) and grow throughout South America. This important compound has been shown to have many different pharmacological effects[2–6] including promising anti-cancer activity.[7] Currently, it is undergoing multiple Phase II clinical trials.

Similar to β-lapachone (**2**), *nor*-β-lapachone (**3**) showed expressive cytotoxicity activity for different human carcinoma cell lines such as KB (human epidermal carcinoma), HeLa (human cervical carcinoma), and HepG2 (human hepatocellular carcinoma)[8] reported by Kongkathip and co-workers. In 2007, Ferreira and co-workers reported cytotoxic activities against six neoplastic cancer cells: SF-295 (central nervous system), HCT-8 (colon), MDAMB-435 (breast), HL-60 (leukemia), PC-3 (prostate), and B-16 (murine melanoma) for new arylamino derivatives of nor-β-lapachone.[9] To date there are no efficient methods for preparing these substances.

The best method for the preparation of **2** and **3** is the acid-catalyzed cyclization of lapachol (**1**), and of *nor*-lapachol (**5**), respectively.[10] The latter compound is also obtained from lapachol (**1**) *via* a two-step Hooker oxidation.[11,12] It should be noted that lapachol (**1**) can be synthetically obtained from 2-hydroxy-1,4-naphthoquinone (lawsone, **4**)[13] by

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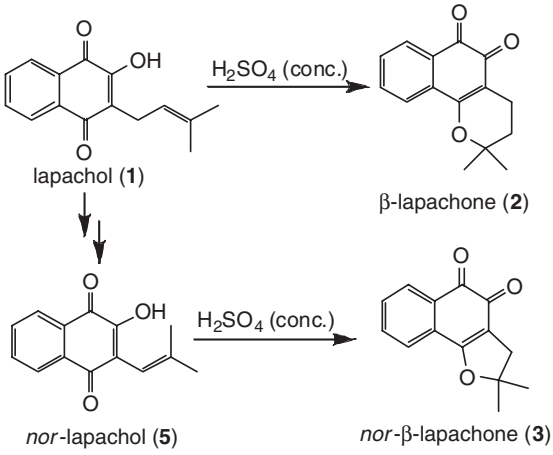
base-induced alkylation with γ,γ-dimethylallyl bromide but this method is very limited due to the formation of O-alkylation product.[14–16]

As continuation of our interest in the chemistry of naphthoquinones and in view of great importance of β-lapachone (**2**) and *nor*-β-lapachone (**3**) against several pharmacological targets, it was decided to develop a synthetic protocol to obtain these substances that could be suitable for scale-up procedures. Herein we describe two effective and efficient processes for their syntheses in a one-pot manner starting from 2-hydroxy-1,4-naphthoquinone (lawsone, **4**).

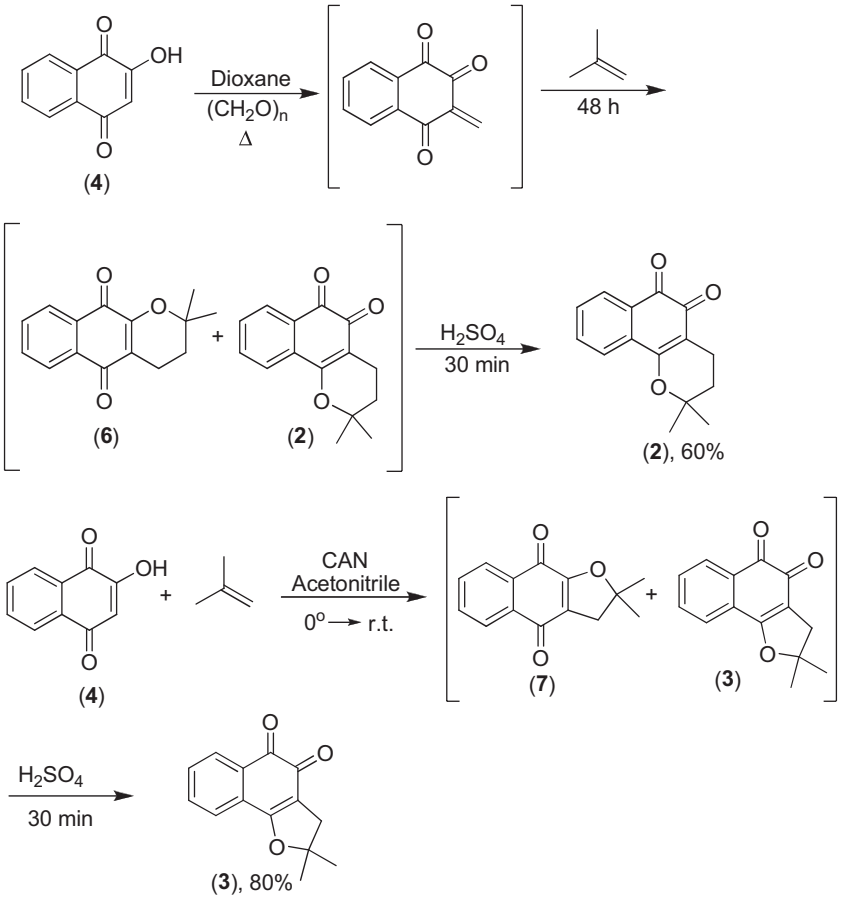
In general, a very useful protocol for the preparation of β-lapachone derivatives is the tandem-Knoevenagel-electrocyclization reactions of **4** with α,β-unsaturated aldehydes producing in one-step dehydro-lapachones, which can be converted into the β-lapachones by acid-catalyzed isomerization followed by hydrogenation of the double bond.[17] Another important and direct methodology for the preparation of the β-lapachone derivatives is the tandem-Knoevenagel/hetero Diels-Alder reactions. This one-pot sequence of reactions involves the Knoevenagel condensation of **4** with aldehydes forming an *ortho*-quinone methide that undergoes hetero Diels-Alder reactions with olefins forming the pyran ring fused with the quinone moeity.[18] The latter protocol was recently improved by Nair and Treesa who reported a new strategy for generating *in situ* an *ortho*-quinone methide[19] intermediate from lawsone (**4**) and paraformaldehyde and its intermolecular hetero Diels-Alder reaction to form pyranonaphthoquinones. Several α- and β-lapachone derivatives were synthesized bythis reaction. However, it was never applied for the preparation of β-lapachone (**2**).

The Knoevenagel condensation of **4** with paraformaldehyde and isobutylene lead to a mixture of 1,2-pyranonaphthoquinone (**2**, β-lapachone) and 1,4-pyranonaphthoquinone (**6,** α-lapachone). Treatment of this crude mixture with conc. sulfuric acid converted it to **2** as the single product in 60% yield (*Scheme 1*).



Scheme 1

The preparation of *nor*-β-lapachone (**3**) was based on radical cyclization of **4** and isobutylene induced by ceric ammonium nitrate (CAN).[20] This reaction leads to a mixture of β- and α-*nor*-lapachone (**7**) which upon treatment with conc. sulfuric acid was converted exclusively to *nor*-β-lapachone (**3**, *Scheme 2*).



Scheme 2

There are certain advantages to prepare **2** and **3** by the procedures summarized in *Scheme 2: (i)* their syntheses were performed in only one step, *(ii)* isolation after acid-mediated isomerization led to the exclusive formation of the desired 1,2-naphthoquinones **2** and **3**, *(iii)* it was demonstrated that it is possible to prepare these compounds using inexpensive, readily available and inexpensive reagents and *(iv)* the preparation of these important substances avoids the use Lapacho trees belonging to threatened ecosystems.

Experimental Section

Reagents were used as purchased without further purification. Lawsone was obtained from Aldrich. Dioxane was dried by distillation from a sodium-benzophenone mixture. Acetonitrile was dried over phosphorus pentoxide. Column chromatography was performed on silica gel 60 (Merck 70–230 mesh). Analytical thin-layer chromatography was performed on silica gel plates (Merck, TLC silica gel 60 F254), and the spots were visualized under UV light or developed by immersion in a solution of ammonium sulfate. Melting point were obtained on Fischer-Johns apparatus and are uncorrected. IR data were recorded as

KBr pellets on a Perkin-Elmer model 1420 FT-IR Spectrophotometer. NMR spectra were determined on a Varian Unity Plus VXR (300 MHz) instrument in $CDCl_3$ solutions. The chemical shift data are reported in δ (ppm) units downfield from tetramethylsilane, used as an internal standard; coupling constants (J) are given in Hertz and refer to apparent peak multiplicities. High resolution mass spectra (HRMS) were recorded on an MICROMASS Q-TOF MICRO Mass spectrometer using ESI-TOF (electrospray ionization-time of flight). The isobutylene gas used in the experiments can be obtained from commercial sources or may be generated *in situ* by dehydration of *tert*-butanol under acid catalysis. [21]

β-Lapachone (2)

To a stirred solution of lawsone (**4**) (0.456 g, 2 mmols) and paraformaldehyde (0.480 g, 16 mmols) in dry dioxane (50 mL) isobutylene gas was bubbled during 18 h. The resulting suspension was stirred at reflux. The progress of the reaction was followed by thin layer chromatography (hexane:ethyl acetate 1:1). Upon consumption of the starting material (*ca.* 48 hours), the mixture was cooled to room temperature and then concentrated sulfuric acid (15 mL) was added and kept stirring for 30 min. The mixture was poured onto ground ice forming a dark orange solid. This solid was collected, dissolved in CH_2Cl_2 (50 mL) and washed with saturated aqueous $NaHCO_3$ (3 × 50 mL). The organic layer was dried over sodium sulfate, filtered, concentrated under reduced pressure and dried under vacuum to give **2** (0.291 g, 60% yield) as an orange solid, mp. 153–155°C, *lit.*[22] 153–155°C. IR (film): 1760 cm^{-1} (C = O); ^{1}H NMR (300 MHz, $CDCl_3$,): δ (J in Hz): 1.47 (6H, s), 1.85 (2H, t, J = 6.8), 2.57 (2H, t, J = 6.8), 7.50 (1H, ddd, J = 8.7, 7.5, 1.2), 7.64 (1H, ddd, J = 9.0, 7.5, 1.4), 7.80 (1H, ddd, J = 7.5, 1.4, 0.4), 8.05 (1H, ddd, J = 7.5, 1.4, 0.4); ^{13}C NMR (75 MHz. $CDCl_3$) δ: 16.3, 26.9, 31.8, 79.5, 112.9, 124.3, 128.7, 130.6, 130.8, 132.8, 135.0, 162.2, 178.7, 180.0. HRMS (ESI): Calcd for $C_{15}H_{14}O_3$: 242.0943. Found: 242.0956.

nor-β-Lapachone (3)

To a stirred solution of lawsone (**4**) (0.456 g, 2 mmols) and cerium (IV) ammonium nitrate (2.74 g, CAN, 5 mmols) in dry acetonitrile (50 mL) was bubbled during 5 h with isobutylene gas and the resulting suspension was stirred at room temperature. The progress of the reaction was followed by thin layer chromatography (hexane:ethyl acetate 1:1). Upon consumption of the starting material (ca. 5 h), concentrated sulfuric acid (10 mL) was added and the mixture was kept stirring for 30 min. The mixture was poured onto ground ice forming a dark orange solid. This solid was collected, dissolved in CH_2Cl_2 (50 mL) and washed with saturated aqueous $NaHCO_3$ (3 × 50 mL) and saturated aqueous NH_4Cl (3 × 50mL). The organic layer was dried over sodium sulfate, filtered, concentrated under reduced pressure and dried under vacuum. Compound **3** (0.387 g, 80% yield) was obtained as an orange solid, mp. 168–170°C, *lit.*[23] 170–171°C. IR (film) 1779 cm^{-1} (C=O); ^{1}H NMR (300 MHz, $CDCl_3$,): δ (J in Hz): 1.53 (6H, s), 2.87 (2H, s), 7.50 (1H, ddd, J = 9.0, 7.3, 1.7), 7.56 (1H, ddd, J = 9.0, 7.3, 2.0), 7.57 (1H, ddd, J = 7.3, 2.0, 0.8), 8.01 (1H, ddd, J = 7.3, 2.0, 0.8); ^{13}C NMR (75 MHz. $CDCl_3$): δ 28.1, 39.0, 93.5, 114.7, 124.3, 127.6, 129.0, 130.6, 131.6, 134.2, 168.6, 175.4, 181.0. HRMS (ESI): Calcd for $C_{14}H_{12}O_3$: 228.0786. Found: 228.0866.

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