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A Preparative Synthesis of Lapachol and Related Naphthoquinones

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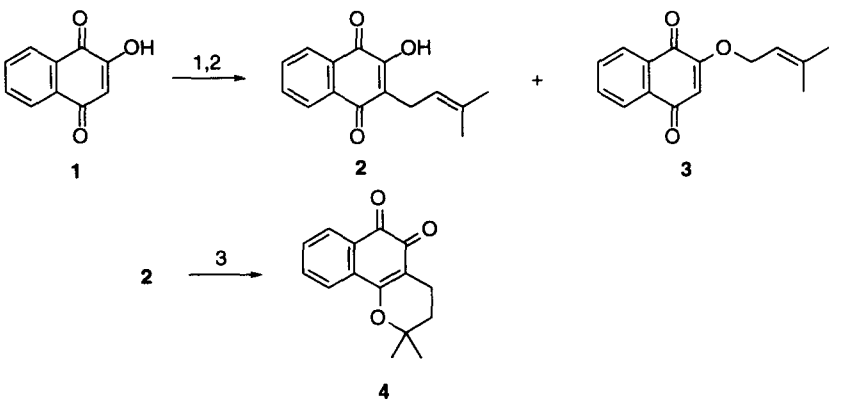
Abstract: The lithium salt of 2-hydroxy-1,4-naphthoquinone was prepared in situ by addition of lithium hydride to the frozen solution of the quinone in dimethyl sulfoxide. As the solution thawed, the lithium quinone was slowly formed and was then alkylated with 3,3-dimethylallyl bromide. Lapachol was thus obtained in 40% yield. When treated with m-chloroperoxybenzoic acid it was converted into its epoxide, that was cyclized with boron trifluoride etherate to 3-hydroxy-β-lapachone in 67% overall yield. Esters of the latter were prepared by condensation with carboxylic acid derivatives using 1,1'-carbonyldiimidazole and DBU as condensing agents.

Keywords: Alkenyl halides; antitumor compounds;lithium hydride; quinones.

β-Lapachone (**4**)[1-3] (Scheme 1) exhibits a number of important pharmacological actions.[4-8] Recent studies have shown that β-lapachone (**4**) induces apoptosis in human prostate cancer cells in vitro.[9,10] Extensive studies on the action of (**4**) and several of its derivatives (e.g. **6**, **9**, **12**, **14**) revealed that they are strong cytotoxic agents.[11,12] We report below on the preparative procedures we used to obtain them in sufficient amounts for biological and clinical studies.



1) i) DMSO, –78 °C, LiH; ii) LiI, $Me_2C{=}CHCH_2Br$, 25 °C; iii) 45 °C, 5 h, H^+. 2) i) EtOAc, 5% $NaHCO_3$, HCl; ii) evap EtOAc, Et_2O, 2 N NaOH, HCl. 3) H_2SO_4, 25 °C, H_2O.

Scheme 1

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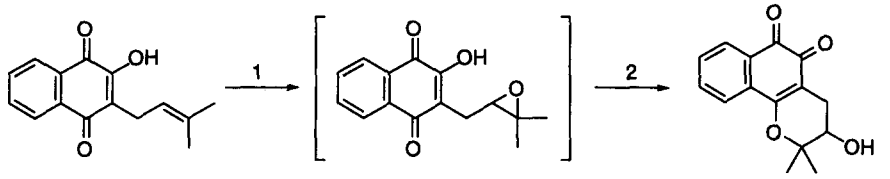
The synthesis of β-lapachone (**4**) and its derivatives **6**, **9**, **12**, and **14** is essentially dependent upon a facile and preparative synthesis of lapachol (**2**). The latter was the target of many synthetic efforts,[13] which in our hands did not give the reported yields. Hence, we developed a procedure based on the alkylation of the lithium salt of 2-hydroxy-1,4-naphthoquinone (**1**) with allyl bromides in dimethyl sulfoxide (DMSO) (Scheme 1). The lithium salt was prepared *in situ* by freezing the solution of **1** in DMSO, then adding lithium hydride, thawing the mixture slowly to allow for a controllable release of hydrogen, and only then proceeding with the alkylation.[14] The cyclization of **2** to **4** is straightforward.[2]



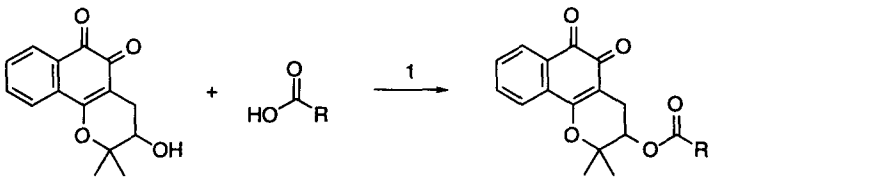
2 **5** **6**

1) *m*-CPBA, CH_2Cl_2, 0 °C, then 25 °C, 17 h, 5% $NaHCO_3$. 2) CH_2Cl_2, BF_3•OEt_2, 25 °C, 21 h, H_2O.

Scheme 2

The synthesis of *3*-hydroxy-β-lapachone (**6**) from **2** required a preparative method. This method was found when **2** was treated with *m*-chloroperoxobenzoic acid. The resulting epoxide **5** was not isolated but cyclized to **6** using boron trifluoride (Scheme 2).[16] By using the Lewis acid, the reported[17,18] spontaneous ring-opening of **5** to give a complex mixture of quinones could be avoided.

Reaction of **6** to give acid, basic, and neutral derivatives involved the activation of a carboxylic reactant using 1,1'-carbonyldiimidazole (CDI), followed by its reaction with **6** in the presence of DBU (Scheme 3). Thus, by condensation of **6** with *t*-butyl acid malonate (**7**) the *t*-butyl ester **8**[19] was obtained; it was then cleaved to the acid derivative **9**[20] by means of trifluoroacetic acid. Condensation of **6** with *N*-BOC-β-alanine (**10**) gave **11** in 50% yield and its deprotection using hydrogen bromide in acetic acid afforded 3-β-alanyloxy-β-lapachone hydrobromide (**12**).[21] Using acetic acid as a reagent, 3-acetyloxy-β-lapachone (**14**)[22] was obtained from **6** in 49% yield.



6

7, R = $CH_2CO_2Bu^t$

10, R = CH_2CH_2NHBOC

13, R = Me

8, R = $CH_2CO_2Bu^t$ ⟵ 2

9, R = CH_2CO_2H

11, R = CH_2CH_2NHBOC ⟵ 3

12, R = $CH_2CH_2NH_3^+Br^-$

14, R = Me

1) i) DMF, CDI (3.0 mmol), RCO_2H (3.0 mmol), 25 °C, 20 min; ii) **6**, (2.0 mmol), DBU (2.6 mmol), 5 h, 25 °C; iii) H_2O, chromatography on silica gel, 30% EtOAc in hexanes. 2) CH_2Cl_2, TFA, 25 °C, 1 h, 50%. 3) 35% HBr/glac. AcOH, 25 °C, 10 min, 47%.

Scheme 3

The alkylation of the lithium salt of **1** with allyl bromides other than dimethylallyl bromide following the general procedure we outlined in Scheme 1, allowed the synthesis of C-alkyl and O-alkyl derivatives analogous to **2** and **3**. The latter were used as intermediates for the synthesis of dunnione and its analogs.[23]

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14. Preparative Synthesis of Lapachol (2): A solution of 2-hydroxy-1,4-naphthoquinone **1** (52.25 g, 300 mmol) in anhydrous DMSO (350 mL) was cooled to –78°C. Lithium hydride (2.50 g, 315 mmol) was added to the solid solution and the solid mixture was allowed to warm slowly to 25°C. Hydrogen was slowly evolved, when it subsided lithium iodide (10 g, 75 mmol) was added followed by 3,3-dimethylallyl bromide (34.6 mL, 300 mmol). The mixture was stirred first at 45°C for 5 h and then at 25°C for further 10 h. The reaction was quenched with ice (200 g) and water (700 mL), after which concentrated HCl (70 mL) was added. The mixture was stirred with ethyl acetate (500 mL), filtered to separate an insoluble solid, the organic layer was separated, the aqueous layer was extracted again wtih ethyl acetate (250 mL), and both ethyl acetate extracts were pooled together. The insoluble solid was dried and crystallized from hexane (20 g, 30%). It was the 2-(3,3-dimethylallyloxy)-1,4-naphthoquinone **3**; mp 150°C (lit[13] mp 149°-150°C); ^{1}HNMR ($CDCl_3$) δ 7.86-7.58 (m, 4H), 6.16 (s, 1H), 4.59 (d, J = 6.8 Hz, 2H), 4.49 (t, J = 6.8 Hz, 1H), 1.81 (s, 3H), 1.76 (s, 3H). The ethyl acetate extracts were washed with 5% aqueous sodium bicarbonate, the latter solution was adjusted to pH 2 with concentrated hydrochloric acid, and the precipitate was filtered and dried. It was the unreacted starting quinone **1** (16.02 g, 30%). The ethyl acetate layer was evaporated to dryness in vacuo. The residue was dissolved in ethyl ether (500 mL), the organic layer was extracted with 2N sodium hydroxide (3 × 200 mL), the pooled alkaline extracts were adjusted to pH 2 with concentrated HCl and cooled. The precipitate was filtered, dried, and crystallized from 75% ethanol; 28.76 g (40%) of lapachol **2** were thus obtained; mp 139°-140°C (lit[13] 136°-137°C; lit[15] 139°-140°C);^{1}HNMR ($CDCl_3$, 300 MHz) δ 8.12 (d, J = 7.5 Hz, 1H), 8.07 (d, J = 7.5 Hz, 1H), 7.75 (t, J = 7.5 Hz, 1H), 7.67 (t, J = 7.5 Hz, 1H), 7.29 (s, 1H), 5.21 (t, J = 7.3 Hz, 2H), 3.31 (d, J = 7.3 Hz, 1H), 1.79 (s, 3H), 1.68 (s, 3H).
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16. Preparative synthesis of **6**: *m*-Chloroperoxybenzoic acid (17.26 g, 70-75%, 70-75 mmol) was added to a solution of lapachol (**2**) (14.35 g, 59.16 mmol) in 300 mL of CH_2Cl_2 while the mixture was kept at 0°C with constant stirring. After 17 h at 25°C, a white precipitate was formed; it was filtered, the filtrate was

extracted with 5% $NaCO_3H$ (300 mL), and the aqueous phase was counterextracted with CH_2Cl_2 (100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was dissolved in anhydrous THF (20 mL) and evaporated in vacuo again. The residue was dissolved in CH_2Cl_2 (250 mL) and $BF_3{\cdot}OEt_2$ (7.6 mL, 60 mmol) was added at 0°C. The solution was then stirred at 25°C for further 21 h, after which water (300 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (100 mL). The combined organic layers were extracted with 5% $NaSO_3H$ three times (2 × 200 mL and 50 mL). The combined $NaSO_3H$ extracts were made alkaline by addition of a saturated K_2CO_3 solution (250 mL) that released **6** from its bisulfite adduct. The brick-red precipitate was filtered and washed with water to give 8.85 g of **6**. The filtrate was extracted with ethyl acetate (3 × 150 mL), the extracts were dried ($MgSO_4$), evaporated in vacuo, and a second batch of **6** was recovered (1.39 g, total yield 67%); mp 202.5°-203.5°C (lit[3] 204-205°C); ^{1}HNMR ($CDCl_3$) δ 8.06 (d, *J* = 7.6 Hz, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 3.92 (m, 1H), 2.83 (dd, *J* = 17.7, 4.8 Hz, 1H), 2.62 (dd, *J* = 17.7, 5.4 Hz, 1H), 1.52 (s, 3H),1.46 (s, 3H).

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19. **8**: ^{1}HNMR (300 MHz, $CDCl_3$) δ 8.10 (d, 1H), 7.84 (d, 1H), 7.68 (t, 1H), 7.55 (t, 1H), 5.22 (t, 1H), 3.33 (s, 2H), 2.95 (dd, 1H), 2.74 (dd, 1H), 1.52 (d, 6H), 1.42 (s, 9H).
20. **9**: mp. 182°-185°C (dec); ^{1}HNMR (300 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.6 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 5.19 (t, *J* = 4.6 Hz, 1H), 3.36 (s, 2H), 2.84 (dd, *J* = 18.2, 4.9 Hz, 1H), 2.73 (dd, *J* = 18.2, 4.4 Hz, 1H), 1.52 (s, 3H), 1.48 (s, 3H). MS-FAB (m/z) 345 (MH^+).
21. **12**: mp 228°-229°C (dec); ^{1}HNMR (300 MHz, D_2O) δ 8.05-7.60 (m 4H), 5.13 (m, 1H), 3.10 (t, *J* = 6.5 Hz, 2H), 2.84 - 2.50 (m, 4H), 1.39 (s, 3H), 1.31 (s, 3H). MS-FAB (m/z) 330 (MH^+).
22. **14**: ^{1}HNMR (300 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.6 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.68 (t, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 5.15 (t, *J* = 4.5 Hz, 1H), 2.82 (dd, *J* = 18.2, 4.8 Hz, 1H), 2.68 (dd, *J* = 18.2, 4.1 Hz, 1H), 2.08 (s, 3H), 1.49 (s, 3H), 1.44 (s, 3H). MS-EI (m/z) 300 (M^+).
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