Synthesis of naturally occurring naphthoquinone epoxides and application in the synthesis of β-lapachone

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Optimized epoxidation conditions of mono- and dialkylated naphthoquinones are presented. Based on the epoxidation protocol making use of H_2O_2/Na_2CO_3, naphthoquinone epoxides are obtained in high yields. The optimized epoxidation conditions are applied in a short and high yielding synthesis of the pharmaceutically important β-lapachone.

Introduction

Quinones and quinone epoxides have been shown to exhibit important biological activities and play an essential role in metabolic processes.[1] The class of quinone epoxides shows important family members from which natural products **1** to **5** are examples (Fig. 1).

Epoxide **1** has been isolated from rubiaceous herbs and is believed to be an intermediate of mollugin biosynthesis.[2] 2-(3-Methylbut-2-enyl)-2,3-epoxy-1,4-naphthoquinone or deoxylapachol epoxide **2** has been shown to exhibit antifungal, antimicrobial, anti-inflammatory, antiparasitic, anticancer and molluscicidal activities.[3] 2,3-Epoxysesamone **3** has been isolated from *Sesamum indicum* (*Pedaliaceae*) and is an antifungal metabolite which has additionally an *anti*-growth activity against human colon carcinoma.[4] Phosphatoquinone A **4**, an antibiotic produced by *Streptomyces sp*., is a potent protein-tyrosine phosphatase inhibitor, an immunosuppressant and an allergy inhibitor.[5] 2,3-Epoxynaphthomevalin A80915G **5** is a member of the napyradiomycin family of antibiotics, isolated from the culture broth of *Chainia rubra* MG802-AF1, which inhibits the growth of gram-positive bacteria including drug-resistant strains.[6] β-Lapachone **6** (Fig. 1) is an orthoquinone which has been isolated from the heartwood of the tropical tree *Tabebuia avellanedae* (Bignoniaceae) and related species.[7,8] β-Lapachone **6** has been reported to exhibit antimicrobial activity.[9] β-Lapachone **6** was found to be cytotoxic to a variety of human cancers.[10] β-Lapachone **6** has recently been under investigation for the treatment of specific cancers associated with elevated NQO1 levels, such as breast, non-small cell lung, pancreatic, colon, and prostate cancers,[11] and is currently

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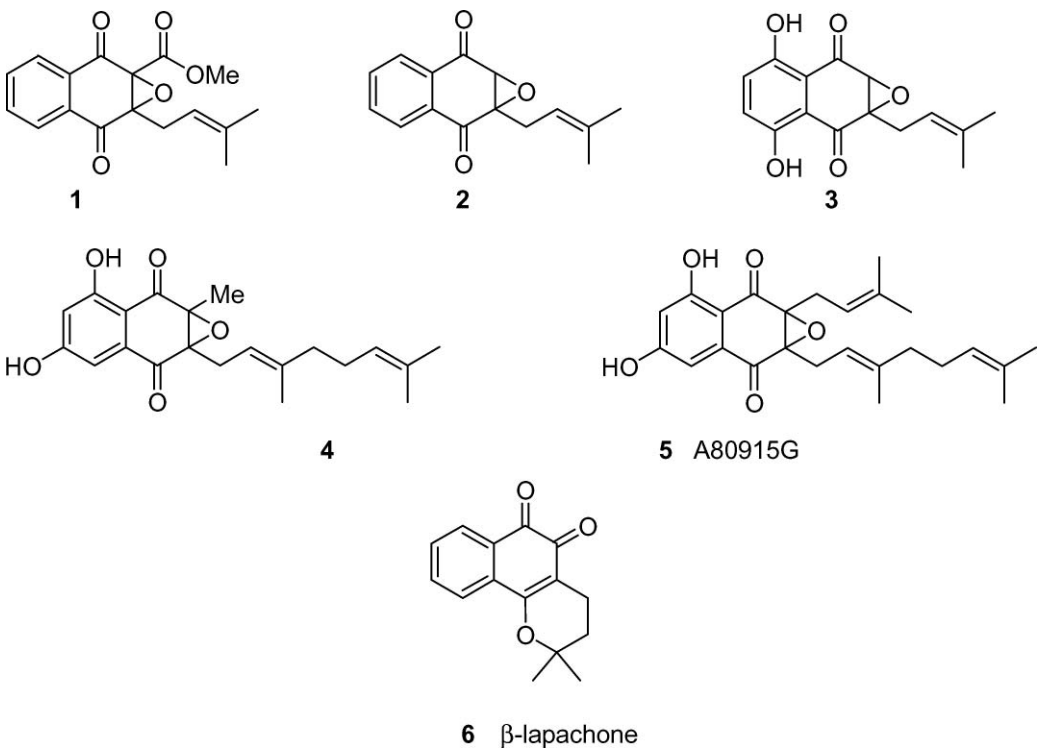


Fig. 1 Important naphthoquinone epoxides.

in phase II clinical trials for the treatment of pancreatic cancer.[12] Particularly promising is the synergistic lethality of β-lapachone with taxol[13] and genistein[14] on several tumour cell lines implanted into mice. Furthermore, β-lapachone **6** has *in vitro* activity against Chagas' disease, caused by *Trypanosoma cruzi*, a parasite infecting about eight million South Americans every year.[15] In the present research, optimized conditions to obtain quinone epoxides are investigated and an application of these quinone epoxides in the synthesis of β-lapachone **6** is presented.

Results and discussion

Screening of the literature shows that epoxidation of 1,4-quinones has been carried out using the urea-hydrogen peroxide complex ($H_2NCONH_2{\cdot}H_2O_2$, UHP).[16] This system has some advantages such as easy handling and easy workup. However, this system has been reported to provide only good yields in reactions with non-substituted 1,4-naphthoquinones.[17]

2,3-Dialkyl-2,3-epoxy-1,4-naphthoquinones can be prepared by NaOCl/pyridine epoxidation[18] whereas monoalkyl-substituted 2,3-epoxy-1,4-naphthoquinones can be prepared by an epoxidation with NaOCl/dioxane.[19] The method by Fieser[20] and the method by Jacobsen and Torssell[18b] focus on the use of the environmentally benign system $H_2O_2/Na_2CO_3/H_2O$. This epoxidation protocol was the starting point of our investigation towards the optimized conditions for the synthesis of novel physiologically important mono- and disubstituted naphthoquinone epoxides.

The method by Fieser,[20] using hydrogen peroxide in ethanol at 40 °C for 5 min, instead of acetone at 0 °C, gave only 10% yield of the targeted natural product and lots of degradation products probably due to further reactions of the formed naphthoquinone epoxide at higher temperatures (Scheme 1).

The method by Jacobsen and Torssell,[18b] using 3 equivalents of 30% aq. H_2O_2 and 1.5 equivalents of Na_2CO_3 in acetone at 0 °C for 40 min, rendered possible the preparation of compound **1** only in 30% along with unreacted starting material.

Subsequently, it was found that the yield of the epoxidation could be increased to 80% by reaction of quinone **7** with 6 equivalents of aq. 30% H_2O_2 and 1.5 equivalents of Na_2CO_3 in acetone and keeping the reaction at 0 °C for 40 min.

Epoxidation of deoxylapachol **8** under the aforementioned conditions using 3 equivalents of aq. 30% H_2O_2 in the presence of 1.5 equivalents of Na_2CO_3 in acetone at 0 °C for 40 min gave a better result of the deoxylapachol epoxide **2** as compared to epoxidation of compound **1** (68% *vs.* 30% yield), presumably because of lower steric hindrance. By the reaction of deoxylapachol **8** with 6 equivalents of aq. 30% H_2O_2 and 1.5 equivalents of Na_2CO_3 in acetone at 0 °C for 40 min, deoxylapachol epoxide **2** was obtained in 82% yield. These conditions are an improvement of the existing method in which deoxylapachol epoxide **2** was obtained using 30% hydrogen peroxide and aqueous sodium hydroxide in toluene in a yield of 53%.[21]

Applying the above reaction conditions for the epoxidation of 2,3-dialkyl-1,4-naphthoquinones **9** and **10**, using 6 equivalents of aq. 30% H_2O_2 and 1.5 equivalents of Na_2CO_3 in acetone at 0 °C, resulted only in starting materials, even after two hours. This result is explained by the electron-donating properties and bulkiness of alkyl groups which hamper the reaction.[21]

The best conditions for the epoxidation of vitamin $K_2(1)$ **9** to afford vitamin $K_2(1)$ epoxide **11** were found to be using 6 equivalents of 30% H_2O_2 and 1.5 equivalents of Na_2CO_3 and heating in ethanol at 45 °C. 2,3-Diprenyl-1,4-naphthoquinone **10** was epoxidized to **12** in 78% yield with 9 equivalents of 30% aq. H_2O_2 and 2.35 equivalents of Na_2CO_3 in ethanol at 45 °C.

Mechanistically, 1,4-naphthoquinones can be considered as electron-deficient olefins and their 2,3-epoxidation can be compared with epoxidation of α,β-unsaturated ketones. The Michael addition of the hydroperoxide anion (HOO^-) to a carbon-carbon double bond of 1,4-quinones is of second order kinetics and is influenced by electronic and steric effects. Electron-donating or bulky substituents such as alkyl groups at C-2 and/or C-3 tend to decrease the rate of epoxidation.[21] On the contrary, transition-state-stabilizing substituents such as phenyl and carbonyl moieties at the 2- and/or 3-positions tend to increase the rate of nucleophilic epoxidation.[22] The observation that the epoxidation gave different yields in acetone as compared to ethanol is ascribed to solubility issues of naphthoquinone and not through *in situ* formation of dimethyldioxirane (DMDO) in acetone. Formation of DMDO should result in epoxidation of olefinic double bonds which is not occurring. Alternatively, the formation of percarbonate by reaction of sodium carbonate with hydrogen peroxide must be taken into account. However the literature reveals that in aqueous solutions this equilibrium reaction is in favor of the dissociated carbonate and hydrogen peroxide.[23]

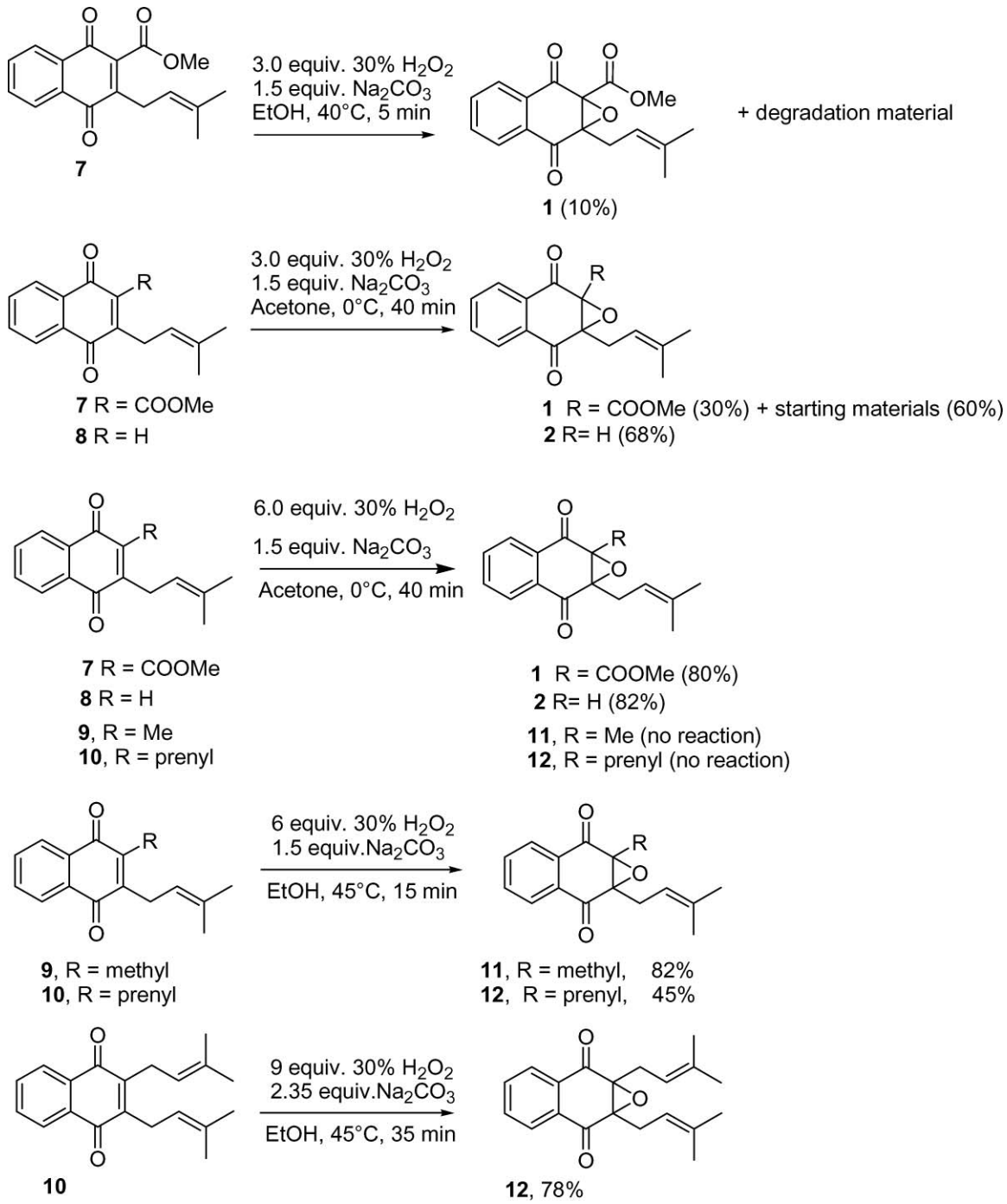
As an application of these synthesized quinone epoxides, a high yielding synthesis of the interesting anticancer natural product β-lapachone **6** was achieved making use of the above mentioned epoxidation reaction to form 2,3-epoxydeoxylapachol **2**.

β-Lapachone **6** has already been synthesized in an eight-step sequence starting from α-naphthol with an overall yield of 23%.[15]

Treatment of lapachol **13** with H_2SO_4 in water has been shown to yield 39% of β-lapachone **6** together with 34% of the isomeric α-lapachone **14** (Scheme 2).[24] Another report has shown that microwave irradiation of lapachol **13** in the presence of montmorillonite clay K10 provided 10% yield of β-lapachone **6** and 70% yield of α-lapachone **14**.[25] Drawbacks of these methods are the limited availability of lapachol **13**, which is obtained in 40% yield starting from 2-hydroxy-1,4-naphthoquinone,[26] and the formation of mixtures of α-lapachone **14** and β-lapachone **6**.

It was reasoned that the reaction of deoxylapachol epoxide **2** with sulfuric acid would lead selectively to β-lapachone **6** without the formation of α-lapachone **14**, if the olefinic double bond is faster activated then the epoxide. Therefore, deoxylapachol epoxide **2** was reacted with 15 equivalents of 96% H_2SO_4, in acetic acid at room temperature for 20 min which cleanly resulted, after aqueous workup, in the formation of β-lapachone **6** in an excellent isolated yield (90%) (Scheme 3).

Mechanistically, two possible routes leading to β-lapachone **6** can be considered (Scheme 4). In route A, the olefinic double bond is first activated. As previously encountered in the synthesis of the natural product mollugin,[2a] this activation easily leads to pyran ring closure with formation of benzochromene intermediate **16**. Subsequently, rearrangement of the epoxide occurs, which leads after keto-enol tautomerism to β-lapachone **6**. Evidence for the rearrangement of the epoxide is found in the related rearrangement of α,β-epoxy-ketones to 1,2-diketones under acidic conditions.[27] An alternative mechanism (Route B) starts with the activation

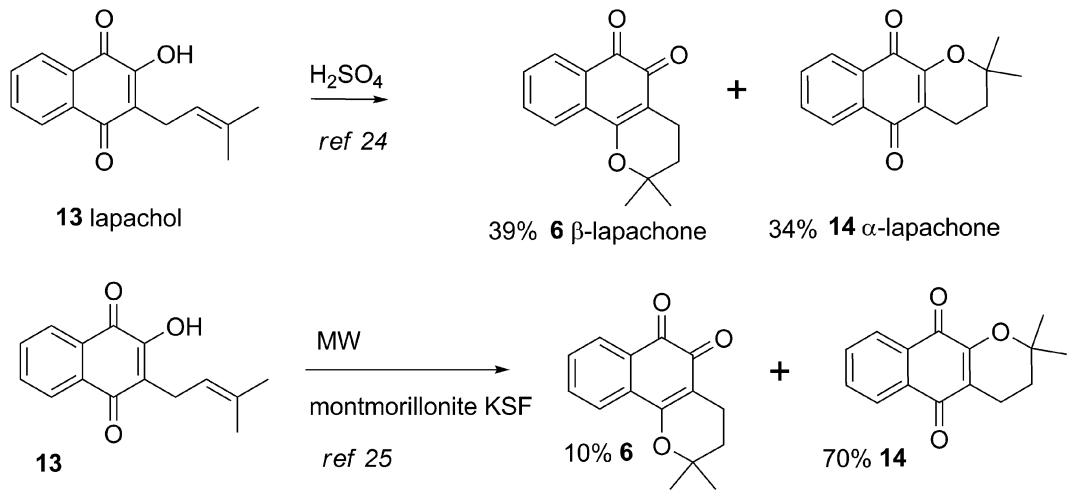


Scheme 1

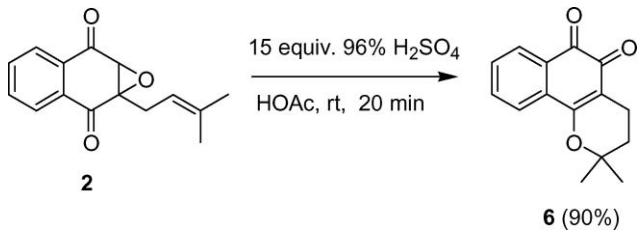
of the epoxide and subsequent rearrangement towards lapachol **13**. Next, the olefinic double bond is activated by protonation, resulting in pyran ring formation. However, from earlier reports it is known that lapachol **13** under acidic conditions leads to the formation of a mixture of α-lapachone **14** and β-lapachone **6**. Therefore, the observation that no α-lapachone **14** and no lapachol **13** was traced back in the reaction mixture, leads to the conclusion that route A was most probably followed. In this way, a very short, high yielding and selective synthesis of the important natural product β-lapachone **6** was established.

Conclusion

The synthesis of 3-(3-methylbut-2-enyl)-2,3-epoxy-1,4-naphthoquinone-2-carboxylate **1** was achieved for the first time *via* a high yielding epoxidation of the corresponding naphthoquinones using hydrogen peroxide as oxidant in acetone at 0 °C in the presence of Na_2CO_3. 2,3-Dialkyl-1,4-naphthoquinones resisted epoxidation with hydrogen peroxide in acetone at low temperature. However, 2,3-dialkyl-1,4-naphthoquinone epoxides are obtained in high yield at 45 °C in ethanol, using an increased



Scheme 2



Scheme 3

amount of hydrogen peroxide. A high yielding, straightforward and selective synthesis of β-lapachone **6** was described by reaction of deoxylapachol epoxide **2** with conc. sulfuric acid in acetic acid. A mechanism of this rearrangement *via* initial pyran ring formation was proposed based on the observance that no α-lapachone **14** and no lapachol **13** were isolated from the reaction mixture.

Experimental part

^{1}H NMR spectra (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Jeol Eclipse FT 300 MHz Spectrometer. IR spectra were recorded on a Perkin-Elmer Spectrum One Spectrometer. Mass spectra were recorded on an Agilent 1100 Series VLL mass Spectrometer (ES 70 eV). Melting points were measured with a Büchi Melting Point B-540 apparatus. Flash chromatography was performed with ACROS silica gel (particles size 0.035–0.070, pore diameter ca 6 nm) using a glass column.

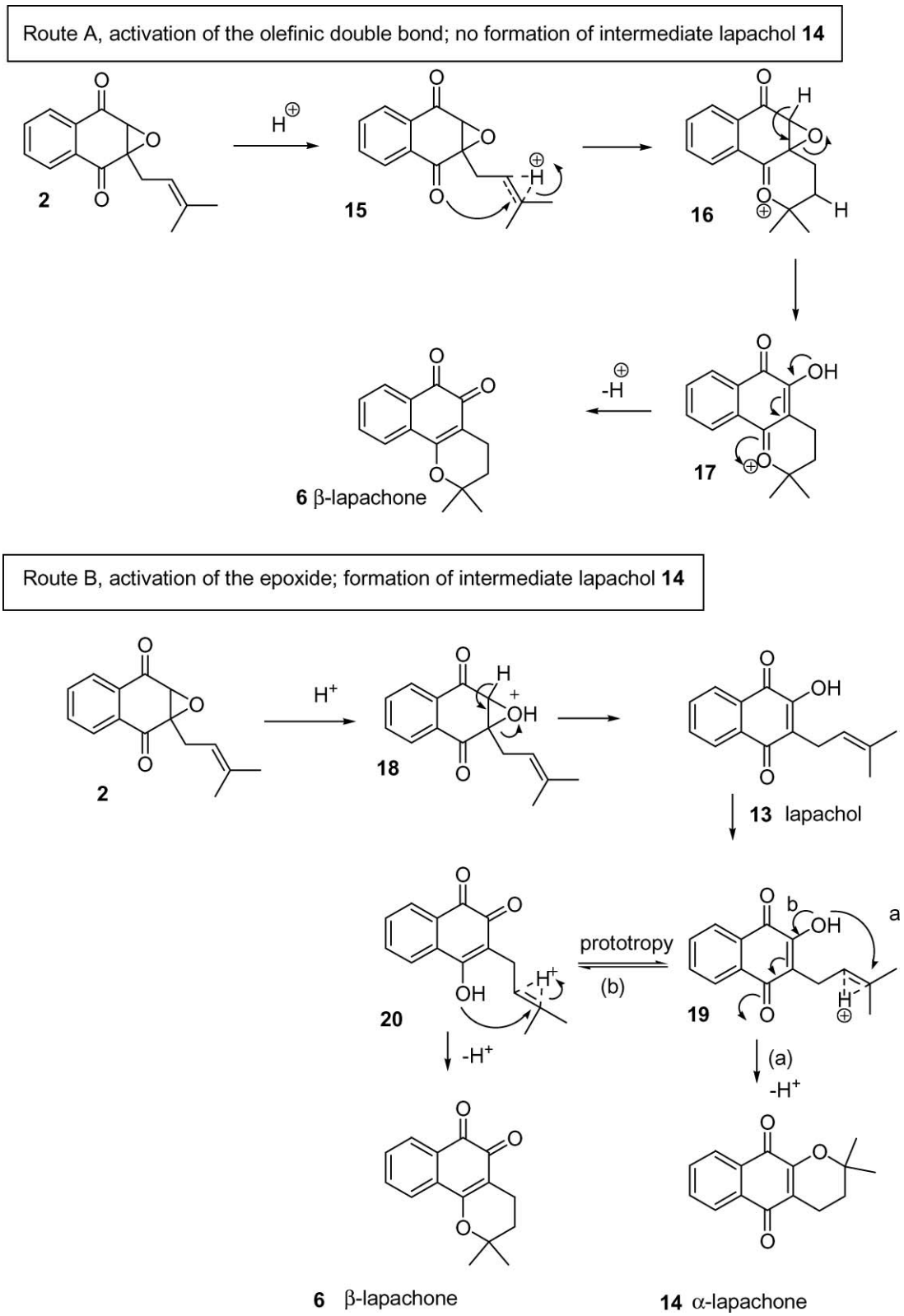
The general procedure for epoxidation of naphthoquinones is exemplified by the synthesis of methyl 3-(3-methyl-but-2-enyl)-2,3-epoxy-1,4-naphthoquinone-2-carboxylate 1

A mixture of methyl 3-(3-methyl-but-2-enyl)-1,4-naphthoquinone-2-carboxylate **7** (0.52 g, 1.83 mmol) in acetone (15 ml) and aqueous Na_2CO_3 (0.39 g, 2.74 mmol, 4 ml H_2O) was cooled at 0 °C, then 30% aq. H_2O_2 (1.25 ml, 10.98 mmol) was slowly added by syringe. The reaction mixture was allowed to stir at 0 °C for 40 min. H_2O_2 was quenched by adding an equivalent amount of 1 M aq. $Na_2S_2O_3$ (11 ml). The resulting mixture was extracted with ethyl acetate, washed 3 times with water, dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by chromatography (petroleum ether/ethyl acetate 9/1) afforded 0.44 g of methyl 3-(3-methyl-but-2-enyl)-2,3-epoxy-1,4-naphthoquinone-2-carboxylate **1** (80%).

Methyl 3-(3-methyl-but-2-enyl)-2,3-epoxy-1,4-naphthoquinone-2-carboxylate 1. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ: 1.70 (6H, s, 2 × CH_3), 2.54 (1H, dd, J = 15.3 Hz, J = 6.4 Hz, CH_aH$_b$), 3.02 (1H, dd, J = 15.3 Hz, J = 7.7 Hz, CH$_a$$H_b$), 3.93 (3H, s, OCH_3), 5.14 (1H, m, CH), 7.77 (2H, m, 2 × CH_{ar}), 8.02 (2H, m, 2 × CH_{ar}). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ: 18.2 (CH_3), 25.9 (CH_3), 26.2 (CH_2), 53.2 (OCH_3), 66.5 (C_{quat}), 115.5 (CH_2–*C*H), 127.4 (CH_{ar}), 127.8 (CH_{ar}), 131.8 (C_{quat}), 131.8 (C_{quat}), 134.7 (CH_{ar}), 135.1 (CH_{ar}), 136.8 (C_{quat}), 163.8 (*C*OOMe), 187.5 (C=O), 189.0 (C=O). **IR** (NaCl) ν_{max}: 1758 (C=O), 1698 (C=O). **MS** (ES$^+$) m/z (%): 301 (M+H$^+$, 100). **Anal. Calcd** for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 70.21; H, 5.48.

2-(3-Methyl-but-2-enyl)-2,3-epoxy-1,4-naphthoquinone 2. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ: 1.69 (3H, s, CH_3), 1.73 (3H, d, J = 0.8 Hz, CH_3), 2.69 (1H, dd, J = 15.4 Hz, J = 6.9 Hz, CH_aH$_b$), 3.03 (1H, dd, J = 15.4 Hz, J = 8.0 Hz, CH$_a$$H_b$), 3.85 (1H, s, OC*H*) 5.08–5.11 (1H, m, CH_2C*H*=), 7.75 (2H, m, 2 × CH_{ar}), 7.92 (CH_{ar}), 7.99 (CH_{ar}). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ: 18.1 (CH_3), 25.9 (CH_3), 26.2 (CH_2), 59.1 (OCH), 63.6 (C_{quat}), 115.5 (=CH), 126.8 (CH_{ar}), 127.5 (CH_{ar}), 132.0 (C_{quat}), 132.4 (C_{quat}), 134.1 (CH_{ar}), 134.3 (CH_{ar}), 137.2 (C_{quat}), 191.8 (C=O), 192.1 (C=O). **IR** (KBr) ν_{max}: 1696 (C=O). **MS** (ES$^+$) m/z (%): 243 (M+H$^+$, 100). **Anal. Calcd** for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.25; H, 6.01.

2-Methyl-3-(3-methyl-but-2-enyl)-2,3 epoxy-1,4-naphthoquinone 11. **^{1}H-NMR** ($CDCl_3$, 300 MHz) δ: 1.71 (3H, s, CH_3), 1.75 (3H, s, CH_3), 1,76 (3H, s, CH_3), 2.42 (1H, dd, J = 15.14 Hz, J = 7.15 Hz, CH_aH$_b$), 3.23 (1H, dd, J = 15.14 Hz, J = 7.15 Hz, CH$_a$$H_b$), 5.10 (1H, m, =CH), 7.71 (2H, m, 2 × CH_{ar}), 7.95 (2H, m, 2 × CH_{ar}). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ: 11.9 (CH_3), 18.2 (CH_3), 25.7 (CH_2), 25.9 (CH_3), 65.1 (C–O), 67.5 (C–O), 117.0 (=CH), 127.0 (2 × CH_{ar}), 132.0 (C_{quat}), 132.2 (C_{quat}), 133.9 (CH_{ar}), 134.2 (CH_{ar}), 135.5 C_{quat}), 192.1 (C=O), 193.0 (C=O). **IR** (NaCl) ν_{max}: 1694 (C=O). MS (ES$^+$) m/z (%): 257 (M+H$^+$, 100). **Anal. Calcd** for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.18; H, 6.47.



Scheme 4

2,3-Bis(3-methyl-but-2-enyl)-2,3-epoxy-1,4-naphthoquinone 12. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 1.71 (6H, s, $2 \times CH_3$), 1.74 (6H, s, $2 \times CH_3$), 2.62 (2H, dd, $J = 15.13$ Hz, $J = 7.15$ Hz, $2 \times CH_aH_b$), 3.06 (2H, dd, $J = 15.13$ Hz, $J = 7.15$ Hz, $2 \times CH_aH_b$), 5.18 (2H, m, $2 \times$ =CH), 7.70 (2H, m, $2 \times CH_{ar}$), 7.95 (2H, m, $2 \times CH_{ar}$). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ: 18.2 ($2 \times CH_3$), 25.9 ($2 \times CH_2$), 26.1 ($2 \times CH_3$), 67.9 ($2 \times C_{quat}$), 117.4 ($2 \times$ =CH), 127.1 ($2 \times CH_{ar}$), 132.2 (C_{quat}), 134.2 ($2 \times CH_{ar}$), 135.2 (C_{quat}), 192.5 (C=O). **IR** (NaCl) ν_{max}: 1695 (C=O). MS (ES$^+$) m/z (%): 311 (M+H$^+$, 100). **Anal. Calcd** for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.72; H, 7.43.

β-Lapachone 6

2,3-Epoxydeoxylapachol **2** (1.5 g, 6.2 mmol) was dissolved in glacial acetic acid (10 ml) and concentrated H_2SO_4 (96%, 10 ml) was added. The resulting mixture was stirred at room temperature for 20 min. The reaction mixture was poured into water and extracted with diethyl ether, washed with 1M sodium hydroxide, dried over $MgSO_4$ and the solvent was evaporated *in vacuo*. Flash chromatography on silica gel with ethyl acetate/petroleum ether (1/9) afforded *β-lapachone* **6** (1.2 g) as an orange powder which crystallizes from petroleum ether/ethyl acetate (1/9) in red needles. The spectral data (^{1}H NMR, ^{13}C NMR, IR, MS) were in agreement with those found in the literature.[7,28]

mp: 152.2–153.7 °C. (Lit.:[28] mp: 154–156 °C) **^{1}H NMR** ($CDCl_3$, 300 MHz) δ: 1.47 (6H, s, $2 \times CH_3$), 1.85 (2H, t, $J = 6.7$ Hz, CH_2), 2.57 (2H, t, $J = 6.7$ Hz, CH_2), 7.50 (1H, m, CH_{ar}), 7.64 (1H, m, CH_{ar}), 7.81 (1H, m, CH_{ar}), 8.06 (1H, m, CH_{ar}). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ: 16.2 (CH_2-4), 26.8 ($2 \times CH_2$), 61.6 (CH_2-3), 79.3 (C_{quat}), 112.7 (C_{quat}), 124.1 (=CH), 128.5 (=CH), 130.2 (=C_{quat}), 130.6 (=CH), 132.6 (=C_{quat}), 134.8 (=CH), 162.0 (=C–O), 178.6 (C=O), 179.9 (C=O). **IR** (NaCl) ν_{max}: 1694 (C=O), 1638 (C=O). **MS** (ES$^+$) m/z (%): 243 (M+H$^+$, 100). **Anal. Calcd** for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.20; H, 5.91.

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