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A mechanistic study on the Hooker oxidation: synthesis of novel indane carboxylic acid derivatives from lapachol†

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The Hooker oxidation is one of the most intriguing transformations wherein lapachol (**1**) is readily converted to norlapachol (**2**) in very good yield. This one-pot reaction involves a very intricate mechanism in which the alkyl side chain of lapachol is shortened by one carbon unit. Previous studies have unequivocally established the involvement of an indane carboxylic acid derivative **3**, as a key intermediate (Hooker intermediate), and its simultaneous conversion to norlapachol (**2**) *via* the oxidative cleavage of vicinol diol and subsequent intramolecular aldol reaction of the resulting keto acid. However, the formation of the key Hooker intermediate **3** from lapachol (**1**) remains ambiguous. The present study has thrown some light on the formation of the key intermediate **3** from lapachol (**1**) *via* benzilic acid rearrangement of the corresponding labile *o*-diquinone intermediate **8** derived from lapachol. The involvement of *o*-diquinone intermediate **8** in the Hooker oxidation has been further established by trapping of this labile intermediate as the corresponding phenazine derivative **9**. The involvement of benzilic acid rearrangement as a key step in the Hooker oxidation is further shown with a variety of *o*-quinones prepared from lapachol (**1**).

Introduction

Lapachol (**1**), a prenyl naphthoquinone and a principal constituent of *Newbouldia laevis*, is widely used in African folk medicine.[1,2] It was first isolated by E. Paterno from *Tabebuia avellanedae* (Bignoniaceae family) in 1882 and later found in many other plant families such as Malvaceae, Verbenaceae, Proteaceae, Leguminosae and Sapotaceae.[3]

Lapachol (**1**) and its derivatives exhibit a wide spectrum of therapeutic activities such as, antiedemic, anti-inflammatory, antimalarial, antitumor, antiviral, bactericidal, and fungicidal.[3] Moreover, atovaquone, a structural analogue of lapachol (**1**), in combination with proguanil is being used in the prevention and treatment of malaria.[4]

Many natural and synthetic naphthoquinone derivatives have been extensively studied due to their ability to interfere with the function of enzymes that are critical for DNA replication in cells.[5] β-Lapachone has been the most extensively studied among the cytotoxic naphthoquinones. Moreover, the semisynthetic nor-β-lapachone and its amino derivatives are also found to show potent antitumor activities against several cancer cell lines.[6] A recent report on a pharmacophore modeling study of lapachol derivatives with cytotoxic activity in human promyelocytic leukemia HL-60 cell line provides a valuable insight in designing new and more potent cytotoxic analogues.[7] The biological activities and mode of action of lapachol and its analogues have become the subject of many synthetic studies (Fig. 1).[8]

The Hooker oxidation is one of the most intriguing reactions in organic chemistry.[9] A historic example is the one pot conversion of lapachol (**1**) to norlapachol (**2**) which involves the degradation of the prenyl side chain by one carbon unit along with the reversal of regiochemistry of the 2-alkyl group and the 3-hydroxy substituent (Scheme 1). Although this one-pot reaction looks simple and takes place readily under mild reaction conditions (1% $KMnO_4$–NaOH, 0 °C), a very intricate mechanism is presumed to be involved.

This unusual reaction accompanied by its interesting features has motivated synthetic organic chemists to explore its mechanistic pathways since the seminal work reported by Hooker. Later, Fieser modified the Hooker oxidation reaction

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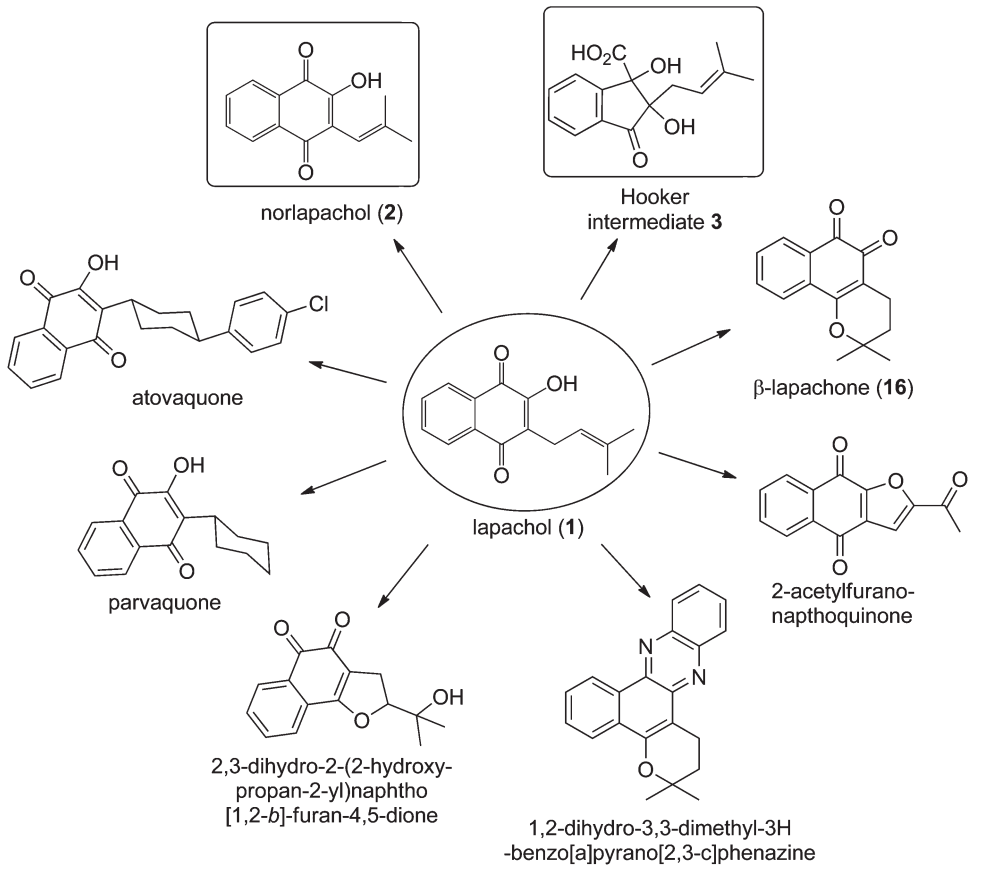
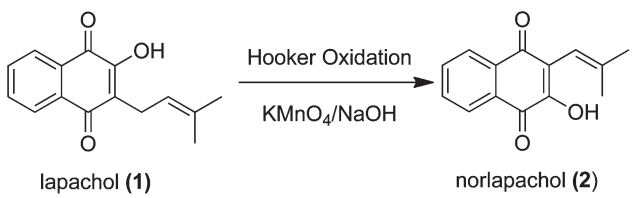
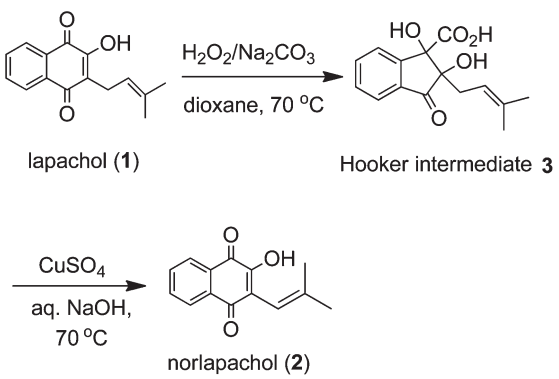


Fig. 1 Biologically active naphthoquinone derivatives from lapachol (**1**).



Scheme 1 Hooker oxidation of lapachol (**1**) to norlapachol (**2**).



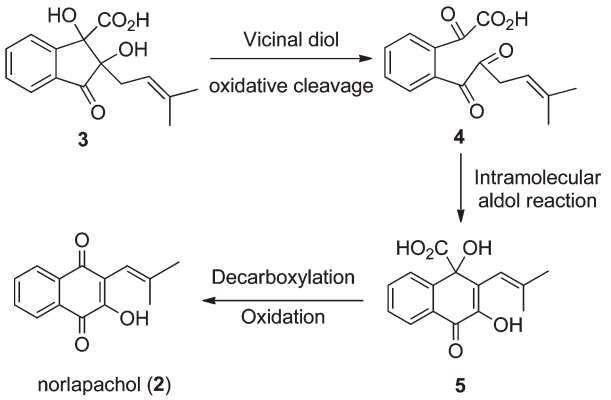
Scheme 2 Hooker oxidation under Fieser's modified conditions.

conditions using a two-step protocol,[10,11] H_2O_2–Na_2CO_3 and $CuSO_4$–NaOH, and showed the involvement of the key intermediate, indane carboxylic acid derivative **3** (Scheme 2).

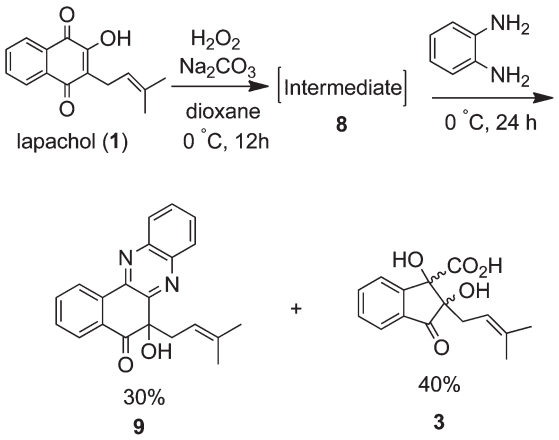
Based on the isolated intermediate **3**, Fieser proposed a novel mechanism for the Hooker oxidation of lapachol (**1**) to norlapachol (**2**) *via* vicinal diol cleavage of the intermediate **3** followed by intramolecular aldol reaction of the resulting triketo-acid **4** and subsequent decarboxylation of the aldol adduct, α-hydroxy acid **5** (Scheme 3).

The mechanism proposed by Fieser was further supported by the ^{13}C-labeling studies carried out by Lee and co-workers which are shown in Scheme 4.[12] Under Hooker oxidation conditions, hydroxynapthoquinone **6**, enriched with ^{13}C at the C1-position of the ethyl substituent, underwent oxidation to furnish hydroxynaphthoquinone **7** wherein the isotopically labeled carbon became part of the naphthoquinone sp^2 carbon. The migration of the ^{13}C-enriched carbon atom from the ethyl side chain to the naphthoquinone ring system of **7** has provided valuable insight into the mechanism of formation of norlapachol (**2**) from the key intermediate **3** during the Hooker oxidation (Scheme 4).

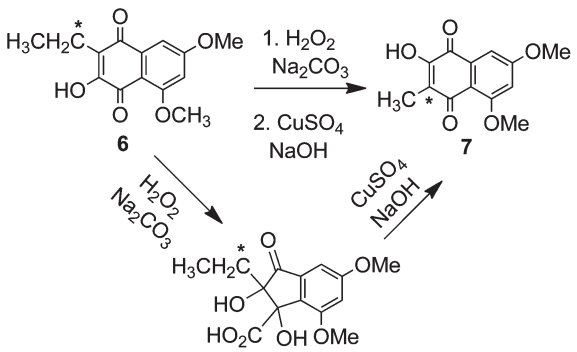
The mechanistic investigation on the Hooker oxidation of lapachol (**1**) to norlapachol (**2**) has unequivocally established the involvement of the key intermediate **3**, and subsequent transformation to norlapachol (**2**). However, the mechanism/mode of formation of the key intermediate **3** from lapachol (**1**) during the Hooker oxidation still remains unclear.



Scheme 3 Proposed mechanism for the Hooker oxidation by Fieser.



Scheme 5 Trapping of labile intermediate **8** with *o*-phenylenediamine.



Scheme 4 ^{13}C Labeling studies on the Hooker oxidation.

Our continued interest in converting lapachol (**1**) to various biologically active and pharmaceutically important molecules recently resulted in the anti-tumor structure activity relationship (SAR) studies of various naphthoquinones derived from lapachol.[13] In the present study, we report a systematic investigation with a variety of examples to demonstrate the involvement of benzilic acid rearrangement[14] as a key step in the Hooker oxidation, leading to the formation of the key intermediate, indane carboxylic acid derivative, **3** from lapachol (**1**).

Results and discussion

Encouraged by the interesting transformation of lapachol (**1**) to norlapachol (**2**), it is of interest to gain deeper insight on the formation of the key intermediate, indane carboxylic acid derivative, **3** from lapachol (**1**) during the Hooker oxidation.

Interestingly, lapachol (**1**) on exposure to Fieser reaction conditions (H_2O_2–Na_2CO_3) at a lower temperature (0 °C) resulted in the formation of a new labile intermediate **8**, which underwent further transformation, under the reaction conditions, to give the Hooker intermediate **3** in good yield (Scheme 5). However, the labile intermediate **8** was trapped as the corresponding phenazine derivative **9** upon exposure to *o*-phenylenediamine (Scheme 5).

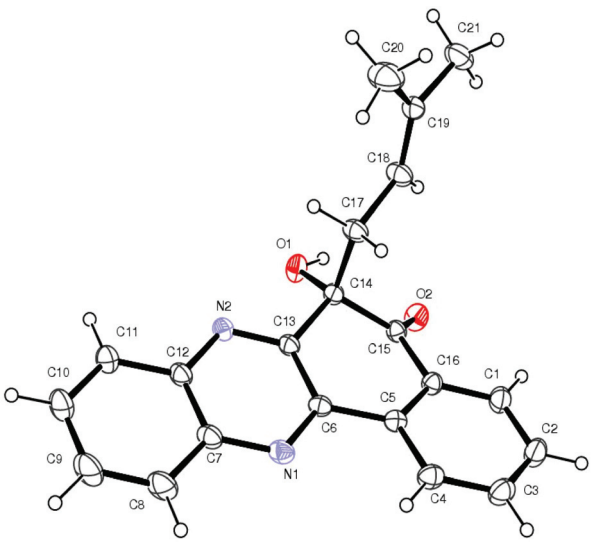
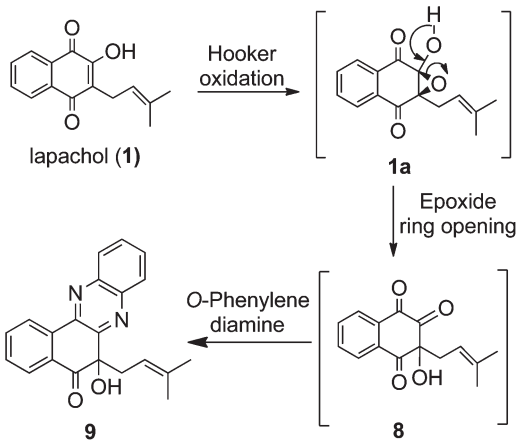


Fig. 2 ORTEP diagram of the phenazine derivative **9**.

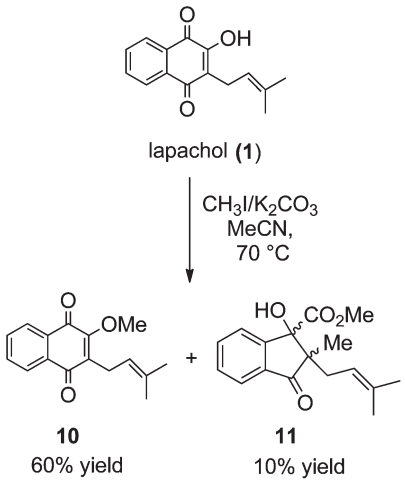
The phenazine derivative **9** was confirmed by ^{1}H, ^{13}C and 2D NMR spectral analyses. In addition, HRMS data for compound **9** is found to be 331.1447, which is in agreement with the calculated mass for a formula $C_{21}H_{19}N_2O_2$. Moreover, the structure of the phenazine derivative **9** is unambiguously confirmed by single crystal X-ray analysis (Fig. 2).[15]

Isolation of the labile *o*-diquinone intermediate **8** as the corresponding phenazine derivative **9** under Hooker oxidation reaction conditions has thrown some light on the mode of formation of the key intermediate **3** from lapachol (**1**) (Scheme 6).

It is anticipated that, during Hooker oxidation, lapachol (**1**) could undergo an epoxidation under basic conditions to form a highly labile quinone epoxy-alcohol intermediate **1a**, which on further isomerisation would lead to base sensitive *o*-diquinone derivative **8**. Exposure of *o*-diquinone derivative **8** to *o*-phenylenediamine would then lead to phenazine derivative **9**. Under basic conditions, in principle, the *o*-diquinone derivative **8** could undergo benzilic acid rearrangement leading to the formation of the key intermediate **3**.



Scheme 6 Plausible mechanism for the formation of *o*-diquinone **8** from lapachol (**1**).



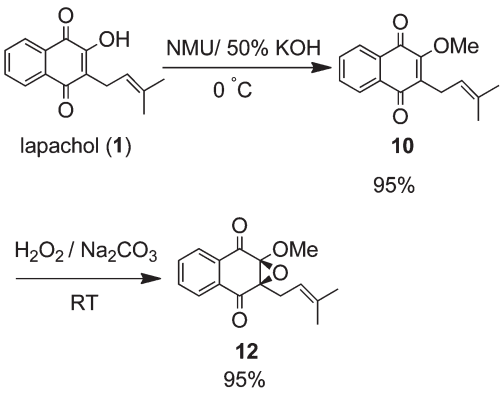
Scheme 7 Methylation of lapachol (**1**) under basic conditions.

To show the involvement of the base-labile *o*-diquinone derivative **8** during the Hooker oxidation of lapachol (**1**) and subsequent transformation to the key intermediate **3**, it is necessary to isolate the highly reactive quinone epoxy-alcohol intermediate **1a** or diquinone **8**. However, all our efforts to isolate the quinone epoxy-alcohol intermediate **1a** under the basic conditions were unsuccessful due to the presence of a free hydroxyl group, which underwent facile epoxide ring opening to give the corresponding equally reactive *o*-diquinone intermediate **8** (Scheme 6).

Hence, it was expected that the protection of free hydroxy group as the corresponding methyl ether derivative would furnish the stable *o*-methylated lapachol derivative **10** by restricting the *in situ* epoxide ring opening and subsequently leading to the key intermediate **3** *via o*-diquinone derivative **8**.

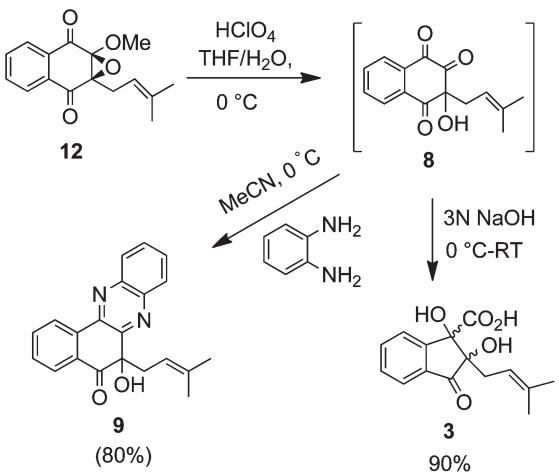
Thus, methylation of lapachol (**1**) using methyl iodide in presence of K_2CO_3 furnished the corresponding *O*-methylated lapachol derivative **10** in 60% yield along with a diastereoisomeric mixture of the indanone ester **11** in 10% yield (Scheme 7). Under these conditions, it is apparent that lapachol (**1**) undergoes Hooker oxidation, leading to the formation of indanone ester **11**.

Conversely, methylation of lapachol (**1**) using diazomethane afforded the *O*-methylated lapachol **10** as the only product in 95% yield (Scheme 8). Interestingly, treatment of the *O*-methylated lapachol derivative **10** under Fieser reaction conditions resulted in the isolation of the expected stable epoxy-quinone ether **12** in 95% yield (Scheme 8).



Scheme 8 Synthesis of epoxy-quinone ether **12**.

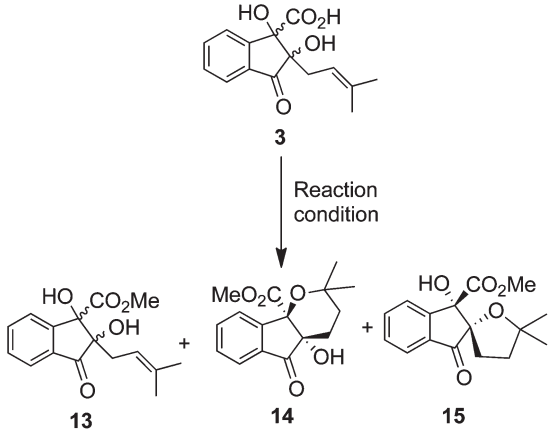
The formation of the epoxy-quinone ether intermediate **12** establishes the involvement of highly reactive quinone epoxy-alcohol intermediate **1a** during Hooker oxidation and subsequent isomerisation to *o*-diquinone derivative **8** (Scheme 6). Further, the acid catalyzed hydrolysis of the epoxy-quinone ether **12** with $HClO_4$ in THF–water medium afforded the highly unstable *o*-diquinone intermediate **8**, which on further exposure to aqueous NaOH, resulted in a smooth rearrangement to give the corresponding Hooker intermediate **3** as a mixture of diastereomers in 90% yield (Scheme 9).



Scheme 9 Trapping of labile intermediate **8** as phenazine derivative **9**.

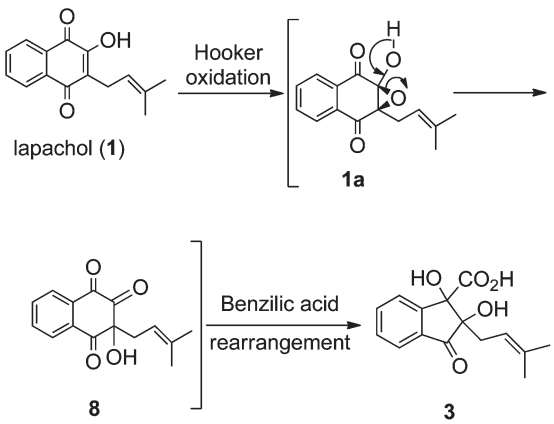
Moreover, the labile compound **8** on treatment with *o*-phenylenediamine, furnished the corresponding phenazine derivative **9** in very good yield (Scheme 9).

Table 1 Esterification of the Hooker intermediate **3**



	Reaction conditions	Yield[a] (%)**13**	Yield[a] (%) **14**	Yield[a] (%) **15**
1	MeOH, PTSA, reflux	5	40	5
2	NMU, KOH, Et_2O	70	—	—

[a] Isolated yield.

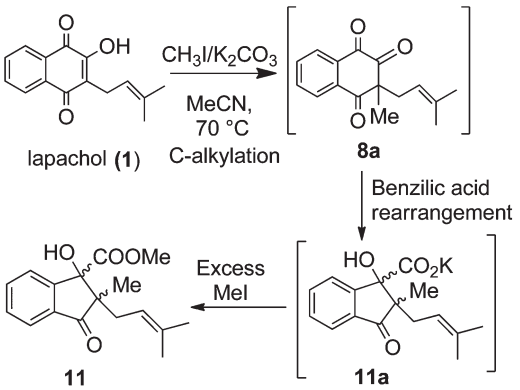


Scheme 10 The role of benzilic acid rearrangement in Hooker oxidation.

The Hooker intermediate **3** was characterized by converting it to the corresponding methyl ester **13.** Exposure of the intermediate **3** to PTSA in MeOH unexpectedly furnished the novel tricyclic ether **14** in 40% yield along with trace amounts of spiroether **15** and methyl ester **13.** However, treatment of intermediate **3** with diazomethane afforded the expected methyl ester **13** in good yield (Table 1).

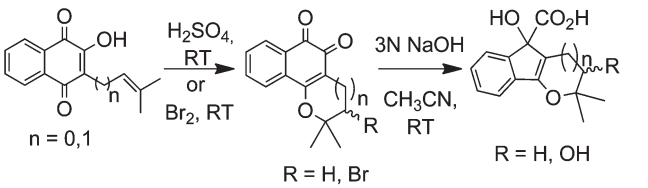
Formation of the key intermediate **3** from *o*-diquinone **8** under basic conditions clearly indicates the involvement of benzilic acid rearrangement as a key step in the Hooker oxidation (Scheme 10).

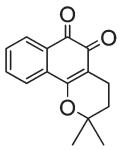
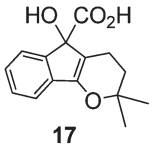
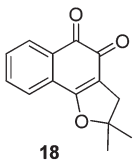
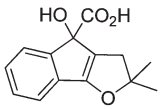
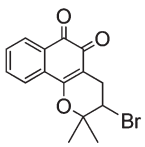
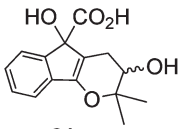
Similarly, the formation of the indanone ester **11** in Scheme 7 can be rationalized based on the benzilic acid rearrangement (Scheme 11). It is likely that the lapachol (**1**) on C-alkylation under basic conditions would lead to *o*-diquinone derivative **8a** which on subsequent benzilic acid rearrangement



Scheme 11 Plausible mechanism for the formation of indanone ester **11** *via* C-alkylation followed by benzilic acid rearrangement.

Table 2 Benzilic acid rearrangement of various *o*-quinones derived from lapachol (**1**)

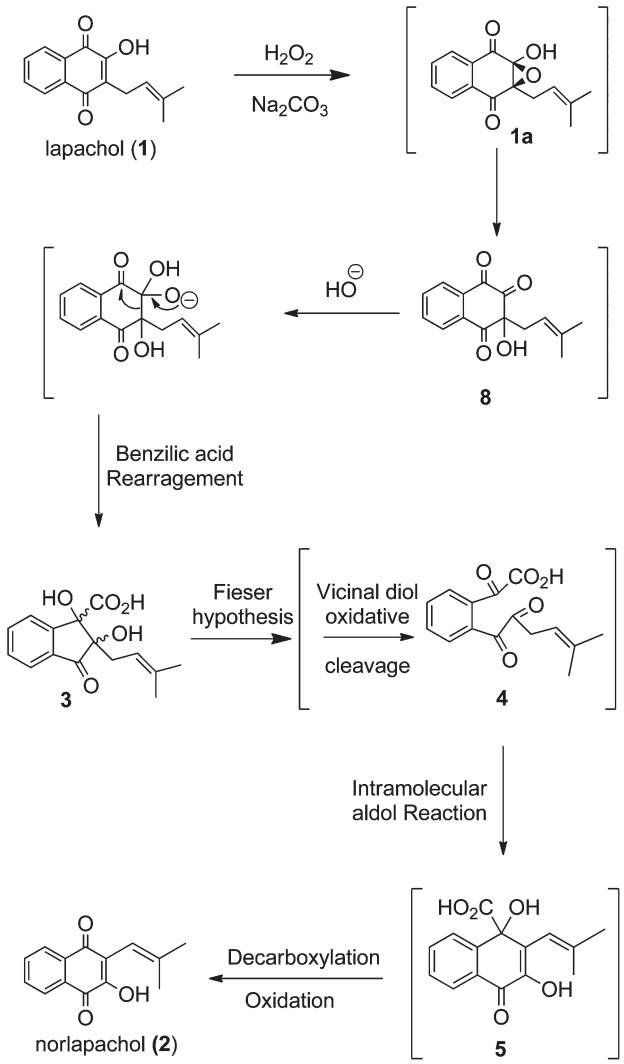


	Substrate	Time (h)	Product	Yield[a] (%)
1	 **16**	10	 **17**	80
2	 **18**	6	 **19**	90
3	 **20**	10	 **21**	70

[a] Isolated yield.

followed by alkylation would lead to the indanone methyl ester **11.**

Moreover, the involvement of the intermediate **8** leading to the formation of the Hooker intermediate **3** *via* benzilic acid rearrangement is further tested with several *o*-quinones derived from lapachol and the results are summarized in Table 2. Following the literature procedure,[7] lapachol upon treatment with conc. H_2SO_4 afforded the β-lapachone (**16**),



Scheme 12 Mechanism for the Hooker oxidation of lapachol (**1**) to norlapachol (**2**).

which on exposure to aqueous NaOH underwent facile benzilic acid rearrangement to give the corresponding 2,3,4,5-tetrahydro-5-hydroxy-2,2-dimethylindeno[1,2-*b*]pyran-5-carboxylic acid **17** in good yield.

Similarly, norlapachol (**2**) on exposure to conc. H_2SO_4 afforded nor β-lapachone **18**, which readily underwent benzilic acid rearrangement under basic conditions to give the corresponding indane carboxylic acid derivative **19** in 90% yield.

The structure of the compounds **17** and **19** were confirmed by the HRMS and 2D NMR spectral analyses. Furthermore, acetylation of lapachol (**1**) followed by bromination of the resulting 2-acetyllapachol afforded 3-bromo-β-lapachone **20**,[7] which on exposure to aqueous NaOH underwent smooth benzilic acid rearrangement to give the corresponding hydroxy-acid **21** in 70% yield (Table 2).

Based on our experimental observations, a plausible mechanism for the Hooker oxidation of lapachol (**1**) to norlapachol (**2**) is delineated in Scheme 12. It is evident from our studies that during the Hooker oxidation under Fieser reaction conditions, the key Hooker intermediate **3** is formed by the benzilic acid rearrangement of the labile *o*-diquinone intermediate **8**. Thus, the lapachol (**1**) would undergo base mediated epoxidation of enone to give quinone epoxy-alcohol **1a** which on subsequent isomerisation would lead to *o*-diquinone intermediate **8**. Under the reaction conditions, the *o*-diquinone intermediate **8** would then undergo benzilic acid rearrangement to afford the key Hooker intermediate **3**. As proposed by Fieser, the key Hooker intermediate **3** on oxidative cleavage followed by intramolecular aldol reaction and subsequent decarboxylation would ultimately lead to the norlapachol (**2**) (Scheme 12).

Conclusion

In conclusion, the mechanism involved in the formation of the Hooker intermediate **3** from lapachol (**1**) *via* benzilic acid rearrangement as a key step has been investigated. Trapping of the labile intermediate **8** as the corresponding phenazine derivative **9** further supports our proposed mechanism. Moreover, the involvement of benzilic acid rearrangement was further tested with a variety of *o*-quinones prepared from lapachol (**1**), which resulted in the formation of novel indane carboxylic acid derivatives. The molecules synthesized during the course of our investigation will be tested for their biological activities in the near future.

Experimental section

Synthesis of 2-hydroxy-3-(2-methylprop-1-enyl)naphthalene-1,4-dione (2)

To a stirred solution of lapachol (**1**) (102 mg, 0.42 mmol) in dioxane–water (6 mL, 3 : 1) was added Na_2CO_3 (54 mg, 0.54 mmol). The resulting mixture was treated with 30% H_2O_2 (0.2 mL) and stirred at 60 °C for 1.5 h, the reaction mass was cooled to 0 °C then treated with 36% HCl (0.5 mL), followed by H_2O and saturated with SO_2, nitrogen gas was purged through the reaction mass for 30 min. Then by 25% NaOH solution (1 mL) and $CuSO_4$ (0.4 g, 2.5 mmol, in 3.5 mL H_2O) were added and stirred at 50 °C for 1 h, the reaction mass cooled to room temperature, filtered through a celite bed, the filtrate was treated with conc. HCl (0.5 mL) to adjust the pH to 2 and extracted with CH_2Cl_2 (3 × 5 mL), dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to give crude compound. Column chromatographic purification of the crude compound over silica gel using 20–30% EtOAc in hexane as solvent gradient afforded pure compound **2** (97 mg, 90% yield) as a yellow solid; IR (neat) 3364, 2928, 1661, 1645, 1593, 1377, 1343, 1325, 1300, 1277 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87–7.80 (m, 2 H), 7.50–7.40 (m, 2 H), 7.25 (bs, 1 H), 5.72 (s, 1 H), 1.72 (d, J = 4.4 Hz, 3 H), 1.40 (d, J = 4.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.8, 181.6, 151.2, 143.7, 134.9, 133.0, 132.9, 129.5, 126.9, 126.1, 120.9, 113.6, 26.6, 21.8;

HRMS (ESI) *m*/*z* calcd for $C_{14}H_{13}O_3$ (M^+ + H) 229.0859, found 228.0858.

Synthesis of 1,2-dihydroxy-2-(3-methylbut-2-en-1-yl)-3-oxo-2,3-dihydro-1*H*-indene-1-carboxylic acid (3)

To a stirred solution of compound **12** (30 mg, 0.11 mmol) in THF–H_2O (3 mL 1 : 1) at 0 °C was added 70% $HClO_4$ (2 μL, 0.2 eq.). The reaction mixture was stirred for 24 h at the same temperature. The crude residue at 0 °C was treated with 3 N NaOH (2 mL) and then stirred for 2 h at room temperature. The resultant mixture was acidified to pH 5 using 5% HCl (2 mL); the solvent was removed under reduced pressure. The residue was diluted with water (5 mL) and CH_2Cl_2 (5 mL), the layers were separated, the reaction mixture was extracted with CH_2Cl_2 (2 × 5 mL), the combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to give the crude product. Column chromatographic purification of the crude compound over silica gel using 5–10% EtOAc in hexane as solvent gradient afforded pure compound **3** (27 mg, 90% yield) as an amorphous material; IR (neat) 3337, 2945, 2834, 1718, 1651, 1386, 1260 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.71–7.63 (m, 3 H), 7.50–7.46 (m, 1 H), 5.08 (m, 1 H), 2.62 (dd, *J* = 14.4, 6.8 Hz, 1 H), 2.16 (dd, *J* = 14.4, 6.8 Hz, 1 H), 1.53 (s, 3 H), 1.37 (s, 3 H); ^{13}C NMR (100 MHz, CD_3OD) δ 207.3, 154.2, 137.7, 137.5, 137.4, 133.0, 131.5, 126.0, 125.2, 120.5, 90.2, 87.5, 36.5 28.0; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{16}O_5Na$ (M^+ + Na) 299.0890, found 299.0890.

Synthesis of 6-hydroxy-6-(3-methylbut-2-enyl)benzo[*a*]-phenazin-5(6*H*)-one (9)

To a stirred solution of compound **12** (100 mg, 0.36 mmol) in THF–H_2O (8 mL, 1 : 1) at 5 °C, was added 70% $HClO_4$ (7 μL, 0.073 mmol). The reaction mixture was stirred for 3 h at the same temperature, then *o*-phenylenediamine (50 mg, 0.5 mmol) dissolved in CH_3CN (1 mL) was added at 5 °C. The reaction mixture was stirred for 3 h, at room temperature, the reaction mixture was diluted with CH_2Cl_2 (5 mL), and extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to give crude compound. Column chromatographic purification of the crude compound over silica gel using 15–25% EtOAc in hexane as solvent gradient afforded pure compound **9** (97 mg, 80% yield) as a crystalline white solid, M. p. 156–158 °C; IR (neat) 3733, 2352, 1684, 1595, 1540, 1455, 1373 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, *J* = 8.0 Hz, 1 H), 8.20–8.17 (m, 1 H), 8.15–8.12 (m, 1 H), 8.06 (d, *J* = 7.6 Hz, 1 H), 7.83–7.74 (m, 3 H), 7.61 (t, *J* = 7.6 Hz, 1 H), 4.92 (t, *J* = 7.6 Hz, 1 H), 4.42 (s, 1 H), 2.66 (d, *J* = 7.6 Hz, 2 H), 1.50 (s, 3 H), 1.14 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ199.0, 153.3, 143.9, 142.2, 141.4, 137.8, 136.1, 135.2, 131.5, 130.8, 130.7, 130.5, 129.5, 129.2, 127.3, 125.7, 116.0, 81.9, 43.2, 25.8, 17.7; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{19}N_2O_2$ (M^+ + H) 331.1441, found 331.1447.

Methylation of lapachol (1)

Lapachol (**1**), (50 mg, 0.20 mmol) in acetonitrile (3 mL) was heated on a steam bath under reflux until it dissolved. The resulting solution was cooled to room temperature and anhydrous potassium carbonate (31 mg, 0.22 mmol) followed by methyl iodide (20 μL, 0.32 mmol) was added at room temperature. The reaction mixture was allowed to reflux for 6 h, the resulting solution was cooled to room temperature and the solvent was removed under reduced pressure. The residue was diluted with water (5 mL) and CH_2Cl_2 (5 mL), the layers were separated; the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to give crude compound. Column chromatographic purification of the crude compound over silica gel using 5–15% EtOAc in hexane as solvent gradient afforded pure compound **10** (32 mg, 60% yield) along with a diastereomeric mixture of methyl 1-hydroxy-2-methyl-2-(3-methylbut-2-en-1-yl)-3-oxo-2,3-dihydro-1*H*-indene-1-carboxylate **11** (6 mg, 10% yield) as a light yellow solid.

Spectral data for 2-methoxy-3-(3-methylbut-2-enyl)-naphthalene-1,4-dione (10)

IR (neat) 2922, 2855, 1661, 1602, 1450, 1333, 1254 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.08–8.04 (m, 2 H), 7.72–7.67 (m, 2 H), 5.15–5.12 (m, 1 H), 4.13 (s, 3 H), 3.31 (d, *J* = 7.0 Hz, 2 H), 1.79 (s, 3 H) 1.69 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) 185.3, 181.8, 157.4, 134.7, 133.7, 133.6, 133.2, 132.0, 131.5, 126.2, 126.0, 120.0, 61.2, 25.8, 23.0, 17.9; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{17}O_3$ (M^+ + H) 257.1172, found 257.1173.

Spectral data for methyl 1-hydroxy-2-methyl-2-(3-methylbut-2-enyl)-3-oxo-2,3-dihydro-1*H*-indene-1-carboxylate (11)

White solid, M. p. 77–79 °C; IR (neat) 3493, 3320, 2925, 1723, 1601, 1456, 1378, 1265, 1188, 743 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 7.5, 1.5 Hz, 1 H), 7.73 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.61 (dd, *J* = 7.5, 1.2 Hz, 1 H), 7.52 (td, *J* = 7.5, 1.2 Hz, 1 H), 5.01 (td, *J* = 7.5, 1.2 Hz, 1 H), 4.22 (s 1 H), 3.61 (s, 3 H), 2.45 (dd, *J* = 7.5, 1.2 Hz, 1 H), 2.05 (dd, *J* = 7.5, 1.2 Hz, 1 H), 1.61 (s, 3 H), 1.45 (s, 3 H), 1.12 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) 206.6, 174.3, 150.0, 136.9, 134.5, 134.1, 129.4, 123.5, 122.9, 118.6, 83.2, 59.7, 53.2, 34.9, 25.6, 17.4, 14.6; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{21}O_4$ (M^+ + H) 289.1434, found 289.1434.

Synthesis of 1a-methoxy-7a-(3-methylbut-2-en-1-yl)-1a,7a-dihydronaphtho[2,3-*b*]oxirene-2,7-dione (12)

To a stirred solution of compound **10**, (60 mg, 0.23 mmol) in dioxane (2 mL) and water (2 mL) at room temperature was added Na_2CO_3 (28 mg, 0.26 mmol). The resulting mixture was treated with 30% H_2O_2 (60 μL) and stirred at room temperature for 1.5 h. The reaction mixture was diluted with saturated brine solution (5 mL) and extracted with CH_2Cl_2 (2 × 5 mL), the combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to give crude compound. Column chromatographic purification of the

crude compound over silica gel using 5–10% EtOAc in hexane as solvent gradient to afford pure compound **12** (60 mg, 95% yield) as a amorphous material; IR (neat) 2921, 2854, 1702, 1596, 1454, 1253, 1017 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06–7.99 (m, 2 H), 7.76–7.72 (m, 2 H), 5.24–5.20 (m, 1 H), 3.85 (s, 3 H), 3.0 (dd, J = 14.5, 7.5 Hz, 1 H), 2.64 (dd, J = 14.5, 6.5 Hz, 1 H), 1.75 (s, 3 H), 1.71 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.1, 189.7, 136.0, 134.5, 134.2, 132.4, 131.6, 127.5, 127.2, 116.8, 85.9, 70.0, 56.9, 25.9, 24.5, 18.1; HRMS (ESI) m/z calcd for $C_{16}H_{17}O_4$ (M^+ + H) 273.1121, found 273.1124.

Methylation of Hooker intermediate (3)

Procedure A. To a stirred solution of 50% KOH (30 mL) in diethyl ether (10 mL) at 0 °C, *N*-nitroso-*N*-methylurea (130 mg, 1.2 mmol) was added gently. The resulting yellow coloured organic layer was separated, dried over KOH pellets and added to compound **3** (50 mg, 0.18 mmol) in ether (5 mL), the reaction mixture was stirred for 2 h and the solvent was removed under reduced pressure. Column chromatographic purification of the crude compound over silica gel using 10–25% EtOAc in hexane as solvent gradient afforded pure compound **13** (70% yield).

Procedure B. To a stirred solution of compound **3** (25 mg, 0.09 mmol) in toluene (5 mL) were added dry methanol (1 mL) and *para*-toluenesulphonic acid (4 mg, 0.018 mmol), the resulting mixture was refluxed with a Dean Stark apparatus for 5 h. After completion of the reaction, the solvent was removed under reduced pressure; the resultant mixture was diluted with EtOAc (7 mL), washed with saturated $NaHCO_3$ solution (2 × 5 mL), water (2 × 5 mL) and brine solution (5 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and then column chromatographic purification of the crude compound over silica gel using 10–25% EtOAc in hexane as solvent gradient afforded pure compounds **13** (5%), **14** (40%) and **15** (5%) yields respectively.

Spectral data for methyl 1,2-dihydroxy-2-(3-methylbut-2-enyl)-3-oxo-2,3-dihydro-1*H*-indene-1-carboxylate (13)

Obtained as white crystalline solid M. p. 148–150 °C; IR (neat) 3606, 3597, 1729, 1368, 1262, 1102 cm^{-1}; ^1H NMR (400 MHz $CDCl_3$) δ 7.78 (d, J = 7.6 Hz, 1 H), 7.69 (dt, J = 7.6, 0.8 Hz, 1 H), 7.62 (d, J = 7.6 Hz, 1 H), 7.53 (dt, J = 7.6, 0.8 Hz, 1 H), 5.06 (qt, J = 6.8, 2.4, 1.2 Hz, 1 H), 4.43 (s, 1 H), 3.62 (s, 3 H), 3.16 (bs, 1 H), 2.74 (dd, J = 14.8, 8.4 Hz, 1 H), 2.10 (dd, J = 14.8, 6.8 Hz, 1 H), 1.64 (s, 3 H), 1.49 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2, 173.0, 148.6, 137.6, 135.5, 135.0, 130.2, 124.3, 123.6, 116.5, 87.5, 83.3, 53.8, 34.0, 26.0, 18.0; HRMS (ESI) m/z calcd for $C_{16}H_{22}NO_5$ (M^+ + NH_4) 308.1493, found 308.3498.

Spectral data for (4a*S*,9b*R*)-methyl 4a-hydroxy-2,2-dimethyl-5-oxo-2,3,4,4a,5,9b-hexahydroindeno[1,2-*b*]pyran-9b-carboxylate (14)

White crystalline solid; M. p. 90–92 °C; IR (neat) 3562, 3386, 1733, 1459, 1375, 1279 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 7.6 Hz, 1 H), 7.63 (dt, J = 7.6, 1.2 Hz, 1 H), 7.57 (d, J = 7.6 Hz, 1 H), 7.52 (dt, J = 7.6, 0.8 Hz, 1 H), 4.41 (bs, 1 H), 3.64 (s, 3 H), 2.45–2.41 (m, 1 H), 1.97–1.88 (m, 3 H), 1.43 (s, 3 H), 1.30 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.8, 173.5, 148.2, 135.6, 135.3, 129.9, 124.2, 123.5, 95.8, 85.0, 82.4, 53.9, 38.3, 33.0, 28.4, 28.1; HRMS (ESI) m/z calcd for $C_{16}H_{18}O_5Na$ (M^+ + Na) 313.1046, found 313.1053.

Spectral data for (1′*S*,2*S*)-methyl 1′-hydroxy-5,5-dimethyl-3′-oxo-1′,3′,4,5-tetrahydro-3*H*-spiro[furan-2,2′-indene]-1′-carboxylate (15)

White crystalline solid, M. p. 160–162 °C; IR (neat) 3562, 3056, 2983, 1731, 1429, 1266 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.82 (td, J = 6.8, 1.2 Hz, 1 H), 7.74 (td, J = 6.4, 0.8 Hz, 1 H), 7.67 (dt, J = 6.0, 4.0 Hz, 1 H), 7.53 (dt, J = 6.0, 0.8 Hz, 1 H), 3.66 (s, 3 H), 3.44 (bs, 1 H), 1.93–1.90 (m, 2 H), 1.78–1.72 (m, 2 H), 1.46 (s, 3 H), 1.0 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.4, 171.5, 135.1, 133.6, 130.1, 125.3, 124.1, 79.4, 74.9, 53.2, 31.1, 29.7, 28.5, 27.5; HRMS (ESI) m/z calcd for $C_{16}H_{18}O_5Na$ (M^+ + Na) 313.1046, found 313.1053.

Synthesis of 2,2-dimethyl-3,4-dihydro-2*H*-benzo[*h*]chromene-5,6-dione (16)[7]

To a stirred solution of lapachol (**1**), (242 mg, 1.0 mmol), was added water (7 mL), followed by conc. H_2SO_4 (0.8 mL, 1.5 mmol), the resulting reaction mixture was stirred for 3 h, at room temperature. The thus obtained orange solid, was filtered and washed with ice cold water (3 × 5 mL), the crude product was dried under vacuum and column chromatographic purification of the crude compound over silica gel using 20–30% EtOAc in hexane as solvent gradient afforded pure compound β-lapachone **16** (97 mg, 40%), as an orange solid; IR (neat) 3526, 3479, 2625, 1726, 1670, 1460, 1361, 1270 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 7.6 Hz, 1 H), 7.80 (d, J = 7.6 Hz, 1 H), 7.63 (t, J = 7.6 Hz, 1 H), 7.49 (t, J = 7.6 Hz, 1 H), 2.55 (t, J = 6.8 Hz, 2 H), 1.84 (t, J = 6.4 Hz, 2 H), 1.45 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.0, 178.7, 162.2, 134.9, 132.7, 130.8, 130.2, 128.7, 124.2, 112.8, 79.4, 31.7, 26.8, 16.2; HRMS (ESI) m/z calcd for $C_{15}H_{15}O_3$ (M^+ + H) 243.1016, found 243.2763.

Synthesis of 2,3,4,5-tetrahydro-5-hydroxy-2,2-dimethylindeno-[1,2-*b*]pyran-5-carboxylic acid (17)

A solution of β-lapachone **16** (50 mg, 0.2 mmol) in acetonitrile (2 mL), at room temperature was treated with 3 N NaOH solution (1 mL). The resultant mixture was stirred for 10 h at room temperature and the mixture was acidified to pH 5 using 5% HCl (2 mL) and the solvent was removed under reduced pressure. The residue was diluted with water (5 mL) and CH_2Cl_2 (5 mL). The layers were separated, the reaction mixture was extracted with CH_2Cl_2 (2 × 5 mL), the combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to give crude compound. Column chromatographic purification of the crude compound over silica gel using 10–20% EtOAc in hexane as solvent gradient afforded pure compound **17** (43 mg, 80% yield) as a reddish amorphous material; IR (neat) 3636, 3470, 1723, 1656, 1460, 1370, 1270 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12–8.05

(m, 2 H), 7.76–7.53 (m, 2 H), 2.71–2.67 (m, 2 H), 1.71–1.67 (m, 2 H), 1.27 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.0, 153.2, 135.0, 133.1, 129.6, 127.1, 126.9, 126.4, 126.3, 124.9, 71.2, 41.7, 36.9, 29.2, 18.5; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{16}O_4Na$ (M^+ + Na) 283.0941, found 283.0946.

Synthesis of 2,2-dimethyl-2,3-dihydronaphtho[1,2-*b*]furan-4,5-dione (18)

To a stirred solution of norlapachol **2** (50 mg, 0.21 mmol) at 0 °C, was added water (2 mL) followed by conc. H_2SO_4 (0.2 mL, 0.31 mmol) and the resultant mixture was stirred for 3 h at room temperature. The reaction mass was diluted with ice cold water (5 mL) and the compound was extracted using CH_2Cl_2 (2 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to give the crude product. Column chromatographic purification of the crude compound over silica gel using 10–15% EtOAc in hexane as solvent gradient afforded pure compound **18** (40 mg, 80% yield) as a red solid; IR (neat) 3526, 3478, 2625, 1726, 1670, 1460, 1356, 1270 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$,) δ 8.06 (d, *J* = 7.6 Hz, 1 H), 7.62 (bs, 2 H), 7.58–7.56 (m, 1 H), 2.93 (s, 2 H), 1.60 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.4, 175.7, 168.8, 134.5, 131.9, 130.9, 129.4, 127.9, 124.6, 115.0, 93.8, 39.3, 28.4; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{13}O_3$ (M^+ + H) 229.0859, found 229.0863.

Synthesis of 3,4-dihydro-4-hydroxy-2,2-dimethyl-2*H*-indeno-[1,2-*b*]furan-4-carboxylic acid (19)

A solution of nor β-lapachone **18** (50 mg, 0.21 mmol) in acetonitrile (2 mL) at room temperature, was treated with 3 N NaOH solution (1 mL) and the resultant mixture was stirred for 6 h at room temperature. The reaction mixture was acidified to pH 5 using 5% HCl (2 mL) and the solvent was removed under reduced pressure. Diluted the residue with water (5 mL) and CH_2Cl_2 (5 mL). Layers were separated, the reaction mixture was extracted with CH_2Cl_2 (2 × 5 mL), combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to give crude compound. Column chromatographic purification of the crude compound over silica gel using 10–20% EtOAc in hexane as solvent gradient afforded pure compound **19** (49 mg, 90% yield) as a yellow crystalline solid; M. p. 94–96 °C; IR (neat) 3526, 3479, 2625, 1726, 1670, 1460, 1361, 1270 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11–8.06 (m, 2 H), 7.76–7.66 (m, 2 H), 2.87 (s, 2 H), 1.30 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.2, 181.2, 155.3, 134.8, 133.5, 132.5, 129.8, 127.0, 126.3, 121.0, 72.8, 36.8, 29.7; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{15}O_4$ (M^+ + H) 247.0965, found 247.0980.

Synthesis of 3-bromo-2,2-dimethyl-3,4-dihydro-2*H*-benzo[*h*]-chromene-5,6-dione (20)[7]

To a stirred solution of lapachol (**1**), (350 mg, 1.44 mmol) in CH_2Cl_2 (8 mL), at 0 °C, 2,6-lutidine (0.33 mL, 2.9 mmol) and acetyl chloride (0.2 mL, 2.9 mmol) were added successively. The resulting reaction mixture was stirred for 3 h, at room temperature. The reaction mixture was concentrated under reduced pressure to give crude compound. Column chromatographic purification of the crude compound over silica gel using 10–20% EtOAc in hexane as solvent gradient afforded pure corresponding acetate derivative of lapachol (43 mg, 80% yield) as a light yellow oil. A solution of acetate derivative of lapachol in CH_2Cl_2 (8 mL) at room temperature, was treated with Br_2 (40 μL, 1.44 mmol) for 10 min. The solvent was removed under reduced pressure to give crude compound. Column chromatographic purification of the crude compound over silica gel using 10–20% EtOAc in hexane as solvent gradient afforded pure compound **20** (440 mg, 95% yield) as a yellow colour solid; IR (neat) 3526, 3479, 2625, 1726, 1670, 1460, 1361, 1270 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (t, *J* = 8.0 Hz, 1 H), 7.81 (t, *J* = 8.0 Hz, 1 H), 7.67 (q, *J* = 7.6 Hz, 1 H), 7.53 (q, *J* = 7.6 Hz, 1 H), 4.29–4.23 (m, 1 H), 3.24–3.16 (m, 1 H), 3.02–2.93 (m, 1 H), 1.63 (d, *J* = 9.6 Hz, 3 H), 1.60 (d, *J* = 9.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.1, 177.9, 161.1, 135.0, 131.6, 131.2, 130.0, 128.8, 124.3, 111.0, 81.1, 49.9, 27.9, 26.1, 23.7.

Synthesis of 2,3,4,5-tetrahydro-3,5-dihydroxy-2,2-dimethylindeno-[1,2-*b*]pyran-5-carboxylic acid (21)

A solution of compound **20** (75 mg, 0.23 mmol) in acetonitrile (2 mL) at room temperature was treated with 3 N NaOH solution (1 mL) and was stirred for 10 h at room temperature. The reaction mixture was acidified to pH 5 using 5% HCl (2 mL) and the solvent was removed under reduced pressure. The reaction mass was diluted with water (5 mL) and CH_2Cl_2 (5 mL). The layers were separated, the reaction mixture was extracted with CH_2Cl_2 (2 × 5 mL), the combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to give crude product. Column chromatographic purification of the crude compound over silica gel using 10–20% EtOAc in hexane as solvent gradient afforded pure compound **21** (45 mg, 70% yield) as a yellow crystalline solid; M. p. 118–120 °C; IR (neat) 3324, 3240, 3058, 1668, 1633, 1345, 1268 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.95 (d, *J* = 7.6 Hz, 2 H), 7.69–7.64 (m, 2 H), 3.56 (dd, *J* = 9.6, 3.3 Hz, 1 H,), 2.77–2.66 (m, 2 H), 1.16 (s, 6 H); ^{13}C NMR (100 MHz, CD_3OD) δ 187.0, 156.2, 134.0, 132.6, 130.3, 125.8, 125.4, 122.2, 77.0, 72.6, 25.5, 24.2, 24.0; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{16}O_5Na$ (M^+ + Na) 299.0889, found 299.0900.

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