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Lewis acid mediated highly regioselective intramolecular cyclization for the synthesis of β-lapachone

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ABSTRACT

A highly regioselective intramolecular cyclization of lapachol mediated by Lewis acids including $NbCl_5$, $AlCl_3$, and $FeCl_3$ was developed for synthesizing β-lapachone in excellent yields without any formation of the isomer α-lapachone. This procedure was efficient, mild, and easily scalable that avoided using highly hazardous concd H_2SO_4. In the case of $ZrCl_4$ the cyclization was found to give α-lapachone as the main product. A possible mechanism for the Lewis acid mediated cyclization was also discussed.

β-Lapachone (**1**) (Fig. 1) is a natural tetrahydropyran-fused *ortho*-naphthoquinone isolated from the Bignoniaceae family (*Tabebuia* sp.).[1] It has been shown to exhibit a wide range of significant biological activities such as antitumor,[2] trypanocidal,[3] anti-inflammatory,[4] antibacterial, and antifungal.[5] Unlike conventional chemotherapeutic agents, β-lapachone (**1**) has been reported to selectively kill human cancer cells through rapid reactive oxygen species (ROS) generation mediated by NAD(P)H:quinone oxidoreductase-1 (NQO1).[6,7] In fact, β-lapachone (**1**) is currently in multiple phase II clinical trials for the treatment of pancreatic cancer.[8] Therefore, it is not surprising that the total synthesis of this pharmaceutically important natural product has attracted great interest in recent decades.

Three synthetic approaches toward β-lapachone (**1**) have been reported as shown in Figure 1. The first one (route A) involved a relatively tedious multistep sequence starting from α-naphthol and provided β-lapachone (**1**) in poor total yields (23–55%).[9,10] The second one (route B) involved an epoxide rearrangement protocol in the presence of 15 equiv of concd H_2SO_4 that led straightly to β-lapachone (**1**) in 90% yield.[11] One disadvantage of this protocol was the limited availability of the key epoxide intermediate, which could be prepared from 1,4-naphthoquinone in two steps with only 29% combined yield.[12] The third and the shortest approach toward β-lapachone (**1**) (route C), involved a protonic acid mediated intramolecular cyclization of lapachol (**2**) through a stable tertiary carbocation intermediate, which was formed by the protonation of the carbon–carbon double bond of the isopentenyl group.[13,14] Lapachol (**2**) could be obtained efficiently from 2-hydroxy-1,4-naphthoquinone in 78% yield.[15] Treatment of lapachol (**2**) with excessive concd H_2SO_4 in water was reported to directly provide 39% yield of β-lapachone (**1**), but together with 34% yield of the isomeric α-lapachone (**3**).[13] While using large amounts of concd H_2SO_4 as both the catalyst and solvent, the cyclization disclosed by ArQule Inc. was shown to provide β-lapachone (**1**) in a multigram scale with over 90% yield.[16] However, the significant excess of concd H_2SO_4 used in these methods was highly hazardous and hard to handle, making them not suitable for industrial-scale production.

Lewis acid catalysis has been of great interest in organic synthesis for efficient carbon–heteroatom bond formation.[17] Recently, in many cases Lewis acid catalysts were found to be effective for the intramolecular cyclization of unsaturated alcohols to give the monocyclic tetrahydropyrans, owing to their ability for the electrophilic activation of the carbon–carbon double bond toward the subsequent attack of a nucleophile.[18,19] Hence, we set out to test the suitability of various readily accessible Lewis acids for the

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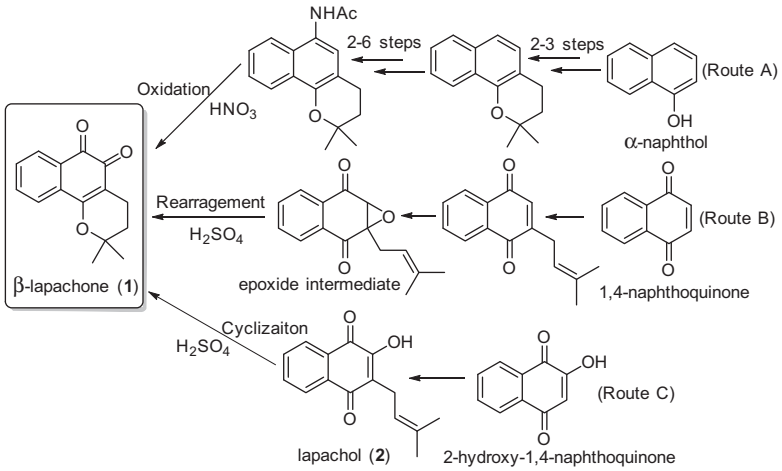
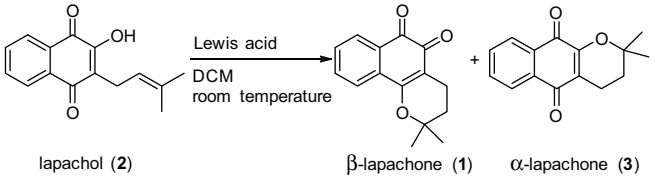


Figure 1. Synthetic approaches to the natural product β-lapachone.

intramolecular cyclization of lapachol (**2**), and to develop a high yielding, regioselective, and scalable procedure for the synthesis of β-lapachone (**1**).

In an initial study we screened various Lewis acids for their effects on the cyclization of lapachol (**2**) to β-lapachone (**1**). The reactions were carried out at room temperature using dichloromethane (DCM) as solvent, which was reported to be the optimal reaction system for the Lewis acid mediated cyclization to tetrahydropyrans.[18] The reaction mixtures were analyzed by high performance liquid chromatography (HPLC) to determine the ratios between the potential products β-lapachone (**1**) and α-lapachone (**3**) as well as their combined yields. As shown in Table 1, many Lewis acids such as $AlCl_3$, $FeCl_3$, BF_3, $BiCl_3$, $NbCl_5$, and $ZrCl_4$ used in 1.5 equiv (Table 1, entries 1–6), were found to be effective to catalyze the cyclization of lapachol (**2**) in 4 h with good to excellent combined yields. But no reaction occurred in the absence of these Lewis acids (data not shown). The reaction provided moderate combined yield when $ZnCl_2$ or $CdCl_2$ was employed (Table 1, entries 7 and 8). Moreover, the reaction rate decreased when treated with $CdCl_2$ (Table 1, entry 7), since a prolonged reaction time was needed to complete this conversion. Some other relatively weak Lewis acids classified by Kobayashi[20] (Table 1, entries 9–14) were shown to be incapable of catalyzing this reaction. These results indicated that the activities of the Lewis acids to promote the cyclization were in remarkable agreement with their acid strength. In addition, it must be emphasized that different regioselectivities were observed in this cyclization by employing different Lewis acids. For instance, when $AlCl_3$, $FeCl_3$, BF_3, and $CdCl_2$ were employed, the reaction was prone to give β-lapachone (**1**) with the β:α ratios ranging from 1:0.20 to 1:0.41 (Table 1, entry 1/2/3/8). While in the presence of $NbCl_5$ or $BiCl_3$, a mixture of the β and α isomers in nearly equal proportions was obtained (Table 1, entry 4/5). Furthermore, in the case of $ZrCl_4$, interestingly, the reaction

Table 1
Intramolecular cyclization of lapachol (**3**) to β-lapachone (**1**) mediated by different Lewis acids in 1.5 equiv[21]



lapachol (**2**) β-lapachone (**1**) α-lapachone (**3**)

Entry[a]	Lewis acid	Reaction time (h)	Selectivity[b] (β:α)	Yield[b] (β+α) (%)
1	$AlCl_3$	4	1:0.41	97
2	$FeCl_3$	4	1:0.20	Quant.
3	BF_3	4	1:0.36	Quant.
4	$BiCl_3$	4	0.79:1	Quant.
5	$NbCl_5$	4	0.86:1	93
6	$ZrCl_4$	4	0.18:1	93
7	$ZnCl_2$	4	0.67:1	80
8	$CdCl_2$	12	1:0.24	79
9	Cu_2Cl_2	12	—	No reaction
10	$CuCl_2$	12	—	No reaction
11	$MnCl_2$	12	—	No reaction
12	$HgCl_2$	12	—	No reaction
13	$NiCl_2{\cdot}6H_2O$	12	—	No reaction
14	$CoCl_2{\cdot}6H_2O$	12	—	No reaction

[a] Reaction conditions: lapachol (0.2 mmol), Lewis acid (1.5 equiv), solvent (DCM, 5 mL), at room temperature.
[b] The selectivity and combined yield were obtained by HPLC analysis of the reaction mixture.

Table 2
The effects of amounts of Lewis acids on regioselectivity of the intramolecular cyclization[21]

Entry[a]	Lewis acid	Loading (Equiv.)	Selectivity[b] (β:α)	Yield[b] (β+α) (%)
1	$AlCl_3$	3	1:0.001	Quant.
2	$AlCl_3$	5	1:0	97
3	$FeCl_3$	3	1:0.002	98
4	$FeCl_3$	5	1:0	98
5	BF_3	3	1:0.46	Quant.
6	BF_3	5	1:0.42	98
7	$NbCl_5$	3	1:0.04	98
8	$NbCl_5$	5	1:0	Quant.
9	$BiCl_3$	3	0.52:1	Quant.
10	$BiCl_3$	5	0.40:1	98
11	$ZrCl_4$	3	0.13:1	Quant.
12	$ZrCl_4$	5	0.14:1	Quant.
13	$BiCl_3$	10	0.33:1	98
14	$ZrCl_4$	10	0.12:1	Quant.
15	$NbCl_5$	4	1:0.002	98
16	$NbCl_5$	2	1:0.74	98
17	$NbCl_5$	0.1	—	No reaction
18[c]	$NbCl_5$	5	1:0	97[d]

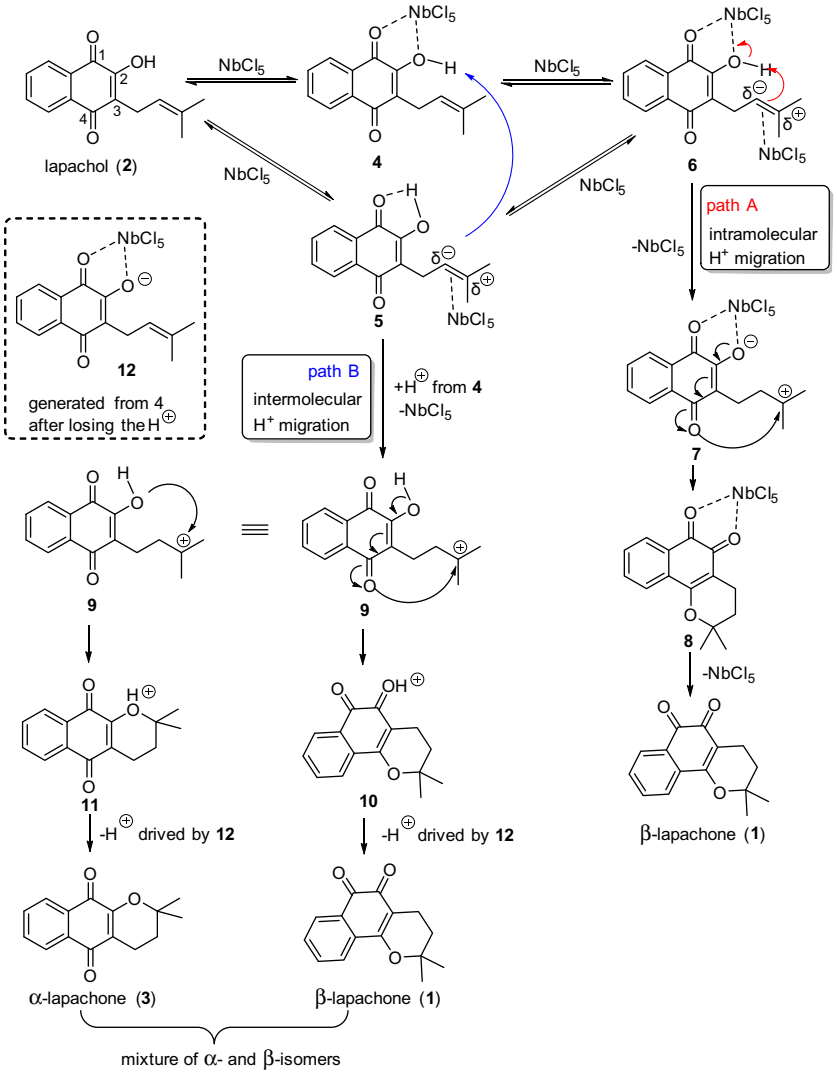
[a] Reaction conditions: lapachol (0.2 mmol), Lewis acid (different equiv), solvent (DCM, 5 mL), at room temperature, for 4 h.
[b] The selectivity and combined yield were obtained by HPLC analysis of the reaction mixture.
[c] Reaction conditions: lapachol (4.13 mmol, 1 g), $NbCl_5$ (20.66 mmol, 5 equiv), solvent (DCM, 50 mL), at room temperature, for 4 h.
[d] Isolated yield.

preferred to produce α-lapachone (**3**) as the main product with a β:α ratio of 0.18:1 (Table 1, entry 6).

Next, to improve the regioselectivity for β-lapachone (**1**), the Lewis acids with high catalytic activities were further tested at different loading amounts (Table 2). An increasing amount of Lewis acid loading from 1.5 to 3 and 5 equiv was initially evaluated (Table 2, entries 1–12). Encouragingly, in the cases of $AlCl_3$, $FeCl_3$, and $NbCl_5$, the β:α ratios of the products were found to be greatly elevated by increasing the amount to 3 and 5 equiv (Table 2, entries 1–4/7–8). Notably, treatment of lapachol (**2**) with these three Lewis acids in 5 equiv led to highly regioselective formation of β-lapachone (**1**) as a single isomer in excellent yields (Table 2, entry 2/4/8). None of the α-lapachone (**3**) was detected by the HPLC analysis of the reaction mixtures. Whereas in the case of BF_3 (Table 2, entries 5 and 6), the amount of Lewis acid loading showed less effect on the regioselectivity and a considerable proportion of the isomer α-lapachone (**3**) was always accompanied with β-lapachone (**1**). For $BiCl_3$, a slight increase in the selectivity for α-lapachone (**3**) was observed as the Lewis acid loading raised from 1.5 to 3 and 5 equiv (Table 2, entries 9 and 10). Further increasing the amount of $BiCl_3$ to 10 equiv made little improvement in the selectivity for α-lapachone (**3**), and the β:α ratio was 0.33:1

(Table 2, entry 13). In a manner similar to $BiCl_3$, when $ZrCl_4$ was employed, the reaction provided a mixture of β and α isomers and the β:α ratio was retained at about 0.1:1 whenever the $ZrCl_4$ loading was changed from 1.5 to 3, 5, and 10 equiv (Table 2, entry 11/12/14). Among these Lewis acids tested, $NbCl_5$ showed the best ability to promote the conversion of lapachol (**2**) to β-lapachone (**1**) with high regioselectivity and quantitative yield (Table 2, entry 8). In order to fully understand the effects of the loading of $NbCl_5$ on the regioselectivity, we carefully decreased its amount from 5 to 4 equiv and a trace of α-lapachone (**3**) was detected with a β:α ratio of 1:0.002 (Table 2, entry 15). Moreover, according to the data (Table 2, entry 8/15/7/16; Table 1, entry 5), there was obviously a downward trend in selectivity for β-lapachone (**1**) as the amount of $NbCl_5$ decreased. Besides, no reaction occurred at low Lewis acid loading in 0.1 equiv (Table 2, entry 17).

Subsequently, with the optimal reaction conditions in hand (Table 2, entry 8), we intended to apply this strategy to the gram-scale synthesis of β-lapachone (**1**). It was shown that a 20-fold scale-up of the reaction still afforded the product in a high 97% isolated yield mediated by 5 equiv of $NbCl_5$ (Table 2, entry 18).[21] This procedure benefits the advantages of high regioselectivity, excellent yield, mild reaction conditions that avoided using highly hazardous concd H_2SO_4, and a convenient post-treatment just by extraction.[22] Therefore, this Lewis acid mediated intramolecular cyclization has great potential for the industrial-scale production of the important *ortho*-quinone natural product β-lapachone (**1**).



Scheme 1. The proposed mechanism for the regioselective formation of β-lapachone (**1**) mediated by Lewis acid $NbCl_5$.

Combining all the results above, we have proposed a possible mechanism for the Lewis acid mediated regioselective intramolecular cyclization by taking $NbCl_5$ as an example (Scheme 1). Firstly, the substrate lapachol (**2**) was likely to form reversibly two possible intermediates **4** and **5**, as it has been reported that some strong Lewis acids could bind bidentately to the adjacent carbonyl and hydroxyl groups[23] and activate the carbon–carbon double bond of the isopentenyl moiety.[18,19] Consequently, the presence of excessive $NbCl_5$ resulted in the formation of the intermediate **6**, which was stabilized by the coordinate interactions with two moles of $NbCl_5$. In view of this, when adequate Lewis acid was employed (5 equiv or more), lapachol (**2**) could be fully converted into the stable intermediate **6**. Then, it underwent the intramolecular proton migration to form the carbocation **7** as shown in path A. The two oxygens at C1 and C2 in the structure of **7** were chelated to one molecule of $NbCl_5$. As a result, the exposed carbonyl group at C4 of **7** was more nucleophilic than the oxygen at C2 and was prior to attack the alkyl cation, leading to the selective formation of the *ortho*-product β-lapachone (**1**) as a single isomer. However, while inadequate Lewis acid was employed (from 1.5 to 4 equiv in our experiments), certain amounts of the intermediates **4** and **5** were probably co-existent with the intermediate **6**. In this case, besides the intramolecular path A, the $NbCl_5$-activated proton of the intermediate **4** could migrate to the $NbCl_5$-activated isopentenyl moiety of the resulting intermediate **5** via an intermolecular pathway as shown in path B. This path led to the activated carbocation **9** without any chelated $NbCl_5$, being different from the carbocation **7**. As previously reported,[11,24] the carbocation **9** could undergo two possible routes involving the intermediates **10** and **11**, which led to the formation of a mixture of β and α isomers. The product **12** generated from intermediate **4** after losing the proton was supposed to serve as the driving force for the intermediates **10** and **11** to lose the proton. This could reasonably explain the observed high selectivity for β-lapachone (**1**) when 5 equiv of Lewis acids such as $NbCl_5$, $AlCl_3$, and $FeCl_3$ were employed, and also explain the observed decreased selectivity while reducing the Lewis acid loading to 4 equiv or less. Besides, in the case of Lewis acid $ZrCl_4$, it mediated the cyclization in an opposite regioselectivity favoring the formation of α-lapachone (**3**). We speculated that $ZrCl_4$ was not strong enough to break the intramolecular hydrogen binding between the carbonyl at C1 and hydroxyl at C2 of lapachol (**2**), but it was capable to interact with the carbonyl at C4, resulting in the selective formation of α-lapachone (**3**). Additionally, we found that the β-lapachone (**1**) and α-lapachone (**3**) failed to convert into each other in the presence of excessive Lewis acids such as $NbCl_5$ and $ZrCl_4$ in our reaction conditions. It suggested that the regioselectivity observed in this Lewis acid mediated cyclization was kinetically controlled, being different from the thermodynamically controlled process mediated by concd H_2SO_4.[24]

In summary, we have presented a highly regioselective cyclization of lapachol (**2**) to β-lapachone (**1**) mediated by Lewis acids including $NbCl_5$, $AlCl_3$, and $FeCl_3$ in excellent yields without any formation of the isomer α-lapachone (**3**). This procedure was efficient, mild, and scalable that avoided using highly hazardous concd H_2SO_4. Thus it has great potential for the industrial-scale production of the important *ortho*-quinone natural product β-lapachone (**1**) and related quinones. In addition, we have found that the regioselectivity was greatly related to the Lewis acid loading. It has also been observed that the cyclization was prior to give α-lapachone (**3**) as the main product when $ZrCl_4$ was employed. We have proposed that Lewis acids promoted the cyclization by activating both the isopentenyl and hydroxyl groups of lapachol (**2**) and the regioselectivity arose from a Lewis acid mediated intramolecular proton migration.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.01.059.

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21. *General procedure for the intramolecular cyclization mediated by Lewis acids.* To a solution of lapachol (**2**) (50 mg, 0.2 mmol) in DCM (5 mL) was added the appropriate amounts of different Lewis acids. The mixture was stirred at room temperature for 4 h or 12 h and then the reaction solution was directly assessed by the HPLC analysis using a mixture of solvent methanol/water (1:3) as the mobile phase. β-Lapachone (**1**): mp 159–160 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.07 (dd, J = 1.8 Hz, 1H), 7.82 (dd, J = 1.8 Hz, 1H), 7.64 (dt, J = 1.8 Hz, 1H), 7.53 (dt, J = 1.8 Hz, 1H), 2.58 (t, J = 6.6 Hz, 2H), 1.86 (t, J = 6.5 Hz, 2H), 1.47 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 179.3, 178.1, 161.5, 134.2, 132.1, 130.1, 129.7, 128.0, 123.5, 112.2, 78.7, 31.1, 26.2, 15.7. HRMS-ESI m/z $[M+H]^+$ calculated for $C_{15}H_{15}O_3$: 243.1016, found: 243.1019. α-lapachone (**3**): mp 116–118 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.06 (m, 2H), 7.68 (m, 2H), 2.62 (t, J = 6.6 Hz, 2H), 1.82 (t, J = 6.5 Hz, 2H), 1.44 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 183.9, 179.5, 154.1, 133.3, 132.4, 131.6, 130.7, 125.8, 125.5, 119.6, 77.6, 30.9, 26.0, 16.2. HRMS-ESI m/z $[M+H]^+$ calcd for $C_{15}H_{15}O_3$: 243.1016, found: 243.1013. The spectroscopic data were identical to those reported in the literature 14.
22. *Procedure for the gram-scale synthesis of β-lapachone (**1**):* To a solution of lapachol (**2**) (1 g, 4.13 mmol) in DCM (50 mL) was added the Lewis acid $NbCl_5$ (5.58 g, 20.66 mmol). The mixture was stirred at room temperature for 4 h. Then the reaction mixture was poured into cooled water (100 mL), extracted with ethyl acetate (3 × 100 mL), and washed with brine (100 mL). The organic layer was combined, dried over sodium sulfate, and concentrated under reduced pressure to give the pure product β-lapachone (**1**) (0.973 g, 97%) without any need for further purification.
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