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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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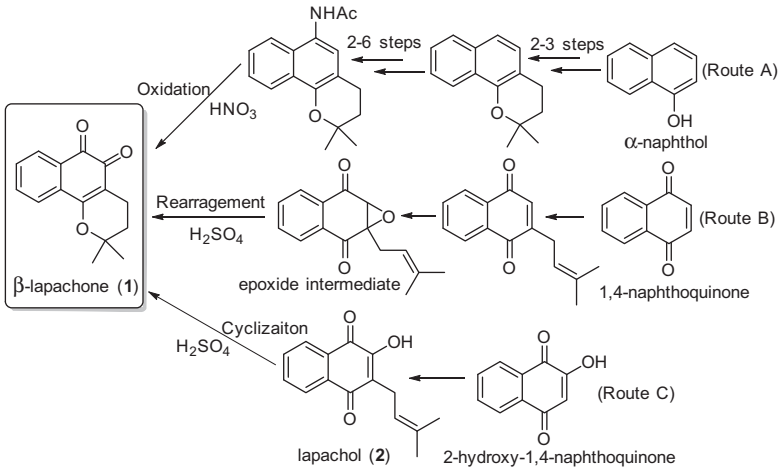
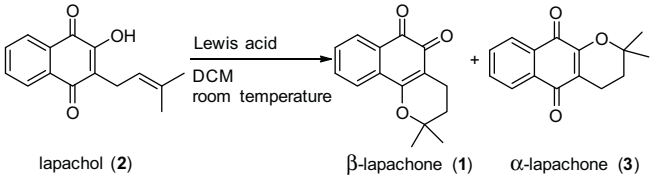


Figure 1. Synthetic approaches to the natural product β-lapachone.

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.