A New, Simple and Efficient Method of Steglich Esterification of Juglone with Long-Chain Fatty Acids: Synthesis of a New Class of Non-Polymeric Wax Deposition Inhibitors for Crude Oil

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A esterificação direta de naftoquinonas mostrou-se uma tarefa difícil. Metodologias mais comuns envolvem a aplicação de cloretos de acila em piridina ou anidridos, entretanto, quando ácidos de cadeia longa são utilizados tais metodologias se mostram ineficientes devido aos baixos rendimentos obtidos. Apresentamos uma nova síntese de ésteres de juglona baseado na esterificação de Steglich utilizando um ácido de Lewis barato como cocatalisador. Rendimentos obtidos são consideravelmente maiores do que os reportados previamente. Química computacional foi utilizada para avaliar os efeitos do CeCl₃ como cocatalisador. Os compostos preparados foram testados como inibidores de deposição de parafinas em petróleo. Éster palmitico da juglona foi capaz de reduzir 4 ºC na temperatura de início de aparecimento de cristais (WAT) do óleo estudado, representando uma redução de 1,5% m/m de parafinas normais precipitadas.

Direct esterification on naphthoquinone presented itself as a hard task. Usual methodologies apply acyl chloride in pyridine or anhydrides but with long-chain esters this procedure proved to be ineffective because of the low yields obtained. We present a new synthesis of long-chain esters of juglone based on Steglich esterification using a cheap Lewis acid as cocatalyst. Yields obtained are considerably better than those found previously. Computational chemistry was used to evaluate the effects of CeCl₃ as cocatalyst. Prepared compounds were tested as wax deposition inhibitors in crude oil. Palmitic ester of juglone was able to lower 4 ºC on the wax appearance temperature (WAT) of the studied oil, representing a reduction of precipitated normal paraffin of 1.5% m/m.

Keywords: juglone, Steglich esterification, fatty acid, wax deposition inhibitor

Introduction

Esterification reaction is one of the oldest, most widely used and most important chemical transformation in organic synthesis, with wide application in chemical industry, pharmaceuticals, food, perfume and cosmetics.¹ This reaction is applied to natural products synthesis, in protection or kinetics resolution of carboxylic acids and in intramolecular reactions to prepare lactones.¹

Since the first reaction presented by Fischer² extensive experimental research and many synthetic methodologies have been developed. In older methods, carboxylic acid was heated in the desired alcohols under acid catalysis, usually employing concentrated sulfuric or hydrochloric acid, phosphorous oxychloride (POCl₃) and sulphonic acids.³

Lewis acids are also catalysts largely applied to esterification reactions, because they allow mild conditions to be used, compared to Brønsted acids. Large amounts of these acids are described in these reactions, such as BF₃·OEt₂, AlCl₃/ZnCl₂, Zn(ClO₄)₂·6H₂O, InCl₃, SnCl₄, TiO(acac)₂, Mn(OAc)₃·2H₂O, Fe₂(SO₄)₃·5H₂O, FeCl₃, NiCl₂·6H₂O, CuCl₂·3H₂O, Cu(OTf)₂, Sc(OTf)₃, ZrCl₂·2THF, HfCl₂·2THF, Zr(OiPr)₄/Fe(OiPr)₃, NbCl₅/Al₂O₃ and I₂, among others.⁴

Solid acids, like zeolites, oxides, aluminoephosphates and their modified forms, are also alternatives employed to substitute traditional catalysis by Brønsted/Lewis acids.⁵

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Another usual methodology is to convert carboxylic acid into acyl halides or anhydride, both more electrophilic forms, in the presence of a base such as triethylamine or pyridine.\(^5\)

Coupling reagents activate the carboxyl group and are therefore broadly used in direct synthesis of alkyl esters, usually with catalytic amounts of 4-dimethylaminopyridine (DMAP). Literature reports include 1,3-dicyclohexylcarbodiimide (DCC),\(^6\) also known as Steglich esterification, di-(2-pyridyl)carbonate,\(^7\) \(O,O'\)-di-(2-pyridyl)thiocarbonate,\(^8\) 2-methyl-6-nitrobenzoic anhydride,\(^9\) 2-dithienylcarbonate (2-DTC),\(^10\) \(N,N'\)-carbonyldiimidazole (CDI),\(^11\) trifluoroacetic anhydride (TFAA),\(^12\) 2-chloro-1-methylpyridinium iodine,\(^13\) CCI\(_4\)/PPh\(_3\),\(^14\) diphenyl(1,2-benzoxazol-3-yl) phosphate,\(^15\) and Me\(_2\)NSO\(_2\)Cl.\(^16\) It is noteworthy that symbiotic activation might also be used to prepare esters. This methodology consists of activating both acid and alkylating agent by use of a reagent that is basic enough to deprotonate the acid, forming a nucleophilic carboxylate and an electrophilic conjugated acid. The use of diazomethane and \(O\)-alkylisourea with carboxylic acids expresses good examples of symbiotic esterification.\(^17\)

In spite of the importance on esterification of phenols, the literature is scarce on preparation of esters of compounds that bear hydroxyl groups directly linked to the naphthoquinone ring, such as juglone (5-hydroxy naphthoquinone) or lawsone (2-hydroxy naphthoquinone). Indeed, the esterification of substituted naphthoquinones having hydroxyl groups or carboxylic acids on side chains is much more common.\(^18\)

The literature presents only a few papers on the direct esterification of the hydroxyl group on juglone.\(^19\) Different methodologies have been applied but all of them show low yields when fatty acids were employed in the preparation of esters. A review is presented on Table 1. We point out the work of Maruo \etal\, that prepared several alkyl esters of juglone with different chain lengths. Three different conditions were employed (entries 1-4).\(^20\) When long-chain acids were used, the standard methodology was to react the respective acyl chlorides with juglone in pyridine, but low yields were obtained (24 and 29%, entries 5-6).\(^21\) Van Duuren \etal\, applied myristoyl chloride with NEt\(_3\) in dry benzene under inert atmosphere to prepare juglone myristic esters in 10% yield after a large number of successive recrystallizations (entry 7).\(^22\)

### Table 1. Juglone esterifications reported in the literature

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>Method</th>
<th>Yield / %</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HO(_2)CMe</td>
<td>A</td>
<td>79</td>
<td>27</td>
</tr>
<tr>
<td>2</td>
<td>HO(_2)CEt</td>
<td>B</td>
<td>64</td>
<td>27</td>
</tr>
<tr>
<td>3</td>
<td>HO(_2)CBu</td>
<td>B</td>
<td>76</td>
<td>27</td>
</tr>
<tr>
<td>4</td>
<td>HO(_2)C(CH(_3))(_3)CH(_2)</td>
<td>B</td>
<td>62</td>
<td>27</td>
</tr>
<tr>
<td>5</td>
<td>HO(_2)C(CH(_3))(_3)CH(_2)C</td>
<td>C</td>
<td>24</td>
<td>27</td>
</tr>
<tr>
<td>6</td>
<td>HO(_2)C(CH(_3))(_3)CH=CH(CH(_3))(_2)CH(_2)</td>
<td>C</td>
<td>29</td>
<td>27</td>
</tr>
<tr>
<td>7</td>
<td>HO(_2)C(CH(_3))(_3)CH(_2)</td>
<td>D</td>
<td>10</td>
<td>28</td>
</tr>
</tbody>
</table>

A: acid anhydride/pyridine; B: carboxylic acid/2-methyl-6-nitrobenzoic anhydride (MNBA)/DMAP/CH\(_2\)Cl\(_2\); C: acyl chloride/DMAP/pyridine/CH\(_2\)Cl\(_2\); D: acyl chloride/Et\(_3\)N/dry benzene/reflux.

Considering the importance of naphthoquinone esters, in this work we developed a new protocol for the Steglich reaction employing CeCl\(_3\), which allowed the synthesis of long-chain juglone esters with superior yields than those described in literature, and applying mild conditions. Esters prepared in this work were also tested as inhibitors of wax deposition in crude oil.

### Results and Discussion

#### Synthesis

Targeting the synthesis of new juglone esters with fatty acids, a large number of methodologies described in the literature were tested. For this study, the reaction between juglone I and palmitic acid 2 was chosen as model because of its intermediate chain size when compared with the other acids used in this work (Scheme 1). Considering that phenol esterification under standard acid catalysis does not present good yields,\(^1\) our first attempt was to promote esterification of I catalyzed by a combination of \(\text{H}_3\text{BO}_3\) and \(\text{H}_2\text{SO}_4\) in toluene under reflux with continuous azotropic distillation of the water formed (Scheme 1, condition a) but it afforded a complex mixture of products.\(^23\) In this case, the use of high temperatures in strong acidic medium and long reaction times may have caused the degradation of...
the starting materials. So, the reaction was carried out in CH₂Cl₂ at room temperature using ultrasound, but no ester was found perhaps by the increase of the ester hydrolysis reaction speed.²⁰

Then we applied kinetic control conditions. In the first tested method, the activation of the carboxyl group by substitution of OH with a better leaving group, such as OTs, used a classic procedure described by Brewster and Ciotti, where TsCl is left to react with the acid in pyridine (Scheme 1, condition b).³⁰ Two mechanistic approaches are described where different intermediates may be formed in situ: first, a mixed anhydride formed by tosyl introduction and second, a symmetric anhydride produced by the attack of a carboxylate anion on the mixed anhydride. After the addition of 1 to the reaction medium, a large number of products were formed making purification extremely complex. This fact may be assigned to the fast decomposition of 1 in basic medium, as reported by Maruo et al.²⁷

In attempt to avoid the use of basic media, we employed the Mitsunobu reaction, a usual methodology to prepare esters from alcohols and phenols under neutral media.³¹ Then, the optimized conditions for the Mitsunobu reaction of phenol reported by Fitzjarrald and Pongdee²³ were applied, where PPh₃, 1 and 2 were dissolved in THF and left to react for 10 min at room temperature. So, DIAD was added and the reaction mixture stirred at room temperature for 72 h. Under these reaction conditions the palmitic acid ester of juglone 3 was obtained in only 7% yield after purification by column chromatography (Scheme 1, condition c). One possible explanation for this result is the low nucleophilicity of juglone and the sensitivity of the Mitsunobu reaction to steric effects.³¹ This reaction, when subjected to reflux conditions, furnished a mixture of products whose separation was fruitless.

Besides the use of activators, we tried to improve the yields obtained by Mitsunobu with application of condensation agents. We first tested CDI in anhydrous DMF (Scheme 1, condition e).³² The reaction proceeds with formation of an acyl imidazolide, which was not isolated since it is highly sensitive to hydrolysis.³² A complex mixture of products was obtained with a small or large excess of CDI (2-5 equiv.). Decomposition may have been caused by formation of imidazole from acyl imidazolide and can therefore, deprotonate the phenolic hydroxyl of juglone with consequent formation of closely related structural isomers.²⁶ During the course of the reaction, fast consumption of the reactants was observed and after 2 h the mixture was isolated and purified, but no ester was found.

Our next step was to change the condensation agent to dicyclohexylcarbodiimide in the presence of DMAP in THF, also known as Steglich esterification (Scheme 1, condition f).²⁶,³²,³³ The procedure was performed at room temperature, affording the juglone ester 3 in only 10% yield in 72 h. This result was obtained after optimization of the reaction conditions, where 2 equiv. of 2 were first allowed to react with 0.4 equiv. of DMAP and 5 equiv. of DCC in THF for 30 min under magnetic stirring. Then, 1 equiv. of 1 was added to the medium.

We believe that the difficulty to produce juglone esters lays on the fact that the 5-OH group causes great sensitivity toward bases and oxidizing agents and forms different related isomers.³⁴ Besides, the possibility of an intramolecular hydrogen bond between 5-OH and 4-C=O induces a significant reduction of the nucleophilicity of the hydroxyl group (Scheme 1).

Considering all methodologies tested, Steglich esterification presented the most significant results, despite low yields. Considering also that the inefficiency of the esterification could result from the low nucleophilicity of naphthoquinone, we investigated the use of CeCl₃·7H₂O in the reaction since it is a very oxophilic Lewis acid, with low toxicity, easy to handle, low cost, stable and recoverable in water.³⁵ Mechanistically, cerium may increase the nucleophilicity of 1 by inhibition of carbonyl tautomerism and/or increase the electrophilicity of the intermediate anhydride formed by complexation.³⁵

In this way, the model reaction was repeated in the presence of DCC/DMAP with different amounts of the catalyst CeCl₃·7H₂O. The best results were obtained using 20 mol% of the Lewis acid where product 3b was obtained in 56% yield after 24 h. This methodology was also applied to other fatty acids such as lauric (2a) and stearic (2c) acids.

Scheme 1. Methodologies applied to the juglone esterification with palmitic acid. Conditions: (a) H₂BO₂, H₂SO₄, toluene, Dean-Stark reflux, 24 h or CH₂Cl₂, ultrasound, r.t.; (b) 1. TsCl, pyridine, 0 ºC; 2. juglone, r.t.; (c) PPh₃, diisopropyldiazodicarboxylate (DIAD), tetrahydrofuran (THF), r.t. or reflux; (d) P₂O₅/SiO₂, 60 ºC, 4-48 h; (e) CDI, THF or CH₂Cl₂ or DMF, r.t., 2 h; (f) DCC, DMAP, THF, r.t., 72 h.
Reaction times and yields are presented in Table 2. All products were purified by column chromatography using silica gel and characterized by infrared (IR), $^1$H and $^{13}$C nuclear magnetic resonance (NMR) spectroscopies.

When compared to other similar esterification reactions employing non-naphthoquinone or even naphthoquinone substrates using carboxylic acids with short alkyl chains, the yields obtained are considerably better when compared with the results of naphthoquinone esterification with fatty acids, described above\textsuperscript{26} (Table 1). It is noteworthy that the methodology developed is much easier than the usual esterifications since, in our procedure, esters were prepared in a single step, in other words, with no need to prepare acyl chlorides and avoiding toxic compounds such as SOCl$_2$ and pyridine.

Aiming to elucidate the catalytic activity of CeCl$_3$·7H$_2$O, computational studies were performed.

### Computational chemistry

To shed some light on the role played by the CeCl$_3$ catalyst in the improvement of naphthoquinone esterification, we calculated the energy of the interaction between the CeCl$_3$ compound and either the juglone $\mathbf{1}$ or acetic anhydride. The goal was to investigate the alternative possibilities for CeCl$_3$ by either increasing the nucleophilicity of the juglone or increasing the electrophilicity of the anhydride. To achieve this, the geometries of the complexes formed when CeCl$_3$ interacts with both the juglone and the anhydride were fully optimized using the semi-empirical SPARKLE/AM1 model\textsuperscript{36} implemented in the MOPAC 2012\textsuperscript{TM} package. SPARKLE/AM1 is the AM1 method\textsuperscript{37} increased with the SPARKLE approach where the lanthanide ion is replaced by a core with $+3$ charge followed by calculation of the electrostatic interactions between the core and the ligands. The SPARKLE/AM1 model has been used to compute a diversity of properties of lanthanide complexes, such as luminescence and absorption spectrum.\textsuperscript{38}

The results show that the enthalpy for the complexation of CeCl$_3$ with the juglone $\mathbf{1}$ is 5.5 kcal mol$^{-1}$ higher, more positive, than for the complexation with acetic anhydride (Scheme 2).

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**Table 2.** Yields and reaction times for juglone esterification

<table>
<thead>
<tr>
<th>Product</th>
<th>Acid</th>
<th>time / h</th>
<th>Yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>$5a$</td>
<td>Lauric (4a)</td>
<td>24</td>
<td>50</td>
</tr>
<tr>
<td>$5b$</td>
<td>Palmitic (4b)</td>
<td>24</td>
<td>56</td>
</tr>
<tr>
<td>$5c$</td>
<td>Stearic (4c)</td>
<td>24</td>
<td>52</td>
</tr>
</tbody>
</table>

---

**Scheme 2.** Complexation energies and partial charges calculated for the cerium complexes.
This shows that complexation of the CeCl$_3$ catalyst occurs preferentially with the anhydride, although a small amount (less than 1%) of complexation with juglone could also be expected at room temperature. In the optimized geometries the Ce(III) ion is placed essentially equidistant from the two oxygen atoms of the ligand, with a closer approximation in the case of the anhydride than in the juglone. The consequence of the CeCl$_3$ molecule complexation with the anhydride is an increased electrophilicity of the corresponding complex, as expressed by the charge densities on the carbon atoms of the carbonyl groups. Charges on both carbon atoms of the carbonyl groups of the anhydride increase from +0.31 to +0.46 e, while for juglone the charges increase from +0.28 e (carbonyl carbon) and +0.28 e (hydroxyl carbon) to +0.44 e (carbonyl carbon) and +0.27 e (hydroxyl carbon). Therefore, the consequences of charge redistribution due to complexation are much stronger in the anhydride than in the juglone. In fact, while an equally large charge variation is observed for both carbons of the anhydride carbonyl, the same is not true for the juglone, on which the charge variation of the hydroxyl carbon atom is much less pronounced than that on the carbonyl carbon, possibly indicating a weaker interaction of the hydroxyl group with the CeCl$_3$.

In summary, our SPARKLE/AM1 computations reveal that the CeCl$_3$ catalyst preferentially interacts with the anhydride increasing its electrophilicity due to delocalization of the negative charge from the carbonyl carbon atoms to the region of contact, to increase the electrostatic interaction with the CeCl$_3$ moiety.

It is then plausible that our reaction may occur by a similar mechanism, as proposed by Khorana and coworkers,$^{33}$ with a new CeCl$_3$ complexation step (Scheme 3). The first steps present the condensation of
DCC (4) with acid 2 catalyzed by DMAP to form the respective anhydride 5. Later, a complexation reaction takes place between the anhydride generated in situ with the Lewis acid producing 6, which may be later attacked by 1 to form ester 3.

**Wax deposition inhibitor activity**

Crude oil is a complex mixture, composed essentially of naphtha, lubricant oil, paraffin and asphalt. Among these chemicals, high molecular weight waxes tend to cause problems due to their tendency of precipitating on pipeline cold walls either during oil production or transportation. Wax deposits inside oil pipelines usually form solid layers that narrow flux passageway, reducing it and eventually causing total blockage and non-programmed stops.

Wax appearance temperature (WAT) is a measure that indicates when the first paraffin crystals start to form. It is extremely important to predict safe operational temperatures to work with cold oil. When external temperatures approach WAT of the oil, high molecular weight waxes form solid deposits leading to flow problems.

Waxy oil A was gently donated by LABPRETO/UFES. Characterization of the crude oil was performed applying the respective American Society for Testing and Materials (ASTM) method presented on Table 3.

**Table 3. Characterization of crude waxy oil A**

<table>
<thead>
<tr>
<th>Property</th>
<th>Method</th>
<th>Oil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free water (v/v)</td>
<td>Decantation</td>
<td>0.0</td>
</tr>
<tr>
<td>BSW (v/v)</td>
<td>ASTM D 4007-02</td>
<td>1.0</td>
</tr>
<tr>
<td>Total BSW (v/v)</td>
<td>ASTM D 4007-02</td>
<td>1.0</td>
</tr>
<tr>
<td>API / degree</td>
<td>ASTM D 7042</td>
<td>35.3</td>
</tr>
<tr>
<td>Density at 20º / (g cm⁻³)</td>
<td>ASTM D 7042</td>
<td>0.8444</td>
</tr>
<tr>
<td>Pour point / ºC</td>
<td>ASTM D 5853-09</td>
<td>42</td>
</tr>
<tr>
<td>NaCl salinity / ppm</td>
<td>ASTM D 6470-99</td>
<td>3185.2</td>
</tr>
<tr>
<td>Sulfur / %</td>
<td>ASTM D 4294</td>
<td>0.07181</td>
</tr>
</tbody>
</table>

BSW: bottom sediment and water; API: American Petroleum Institute gravity.

Then, inhibitory activity on wax precipitation was evaluated for compounds 3a-c by the onset of the first exothermic event observed on the cooling thermogram generated by differential scanning calorimetry (DSC). WAT of samples with different concentrations of 3a-c (50, 100 and 200 ppm) were compared with crude oil without any additive (Table 4).

**Table 4. Calorimetric data for products 3a-c as a function of concentration**

<table>
<thead>
<tr>
<th>entry</th>
<th>Product</th>
<th>Concentration / ppm</th>
<th>WAT / ºC</th>
<th>Wax deposition / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Blank</td>
<td>–</td>
<td>66.38</td>
<td>10.75</td>
</tr>
<tr>
<td>2</td>
<td>3a</td>
<td>50</td>
<td>64.58</td>
<td>10.46</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100</td>
<td>64.64</td>
<td>10.93</td>
</tr>
<tr>
<td></td>
<td></td>
<td>200</td>
<td>64.82</td>
<td>10.49</td>
</tr>
<tr>
<td>3</td>
<td>3b</td>
<td>10</td>
<td>66.38</td>
<td>10.75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50</td>
<td>65.85</td>
<td>11.15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100</td>
<td>62.61</td>
<td>9.36</td>
</tr>
<tr>
<td></td>
<td></td>
<td>200</td>
<td>62.29</td>
<td>9.49</td>
</tr>
<tr>
<td></td>
<td></td>
<td>300</td>
<td>67.90</td>
<td>13.40</td>
</tr>
<tr>
<td>4</td>
<td>3c</td>
<td>50</td>
<td>66.37</td>
<td>12.31</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100</td>
<td>66.51</td>
<td>12.26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>200</td>
<td>67.98</td>
<td>13.46</td>
</tr>
</tbody>
</table>

On the other hand, compound 3b showed a severe improvement on efficiency with higher concentrations, reaching its maximum at 200 ppm where it reduced 4 ºC on WAT.

Ester 3c, however, presented no inhibitory activity, acting as a nucleus of precipitation, raising almost 2 ºC on WAT. This can be explained based on the size of the alkyl chain. This ester bears the longest hydrophobic chain (18 carbons); at this point, the hydrophobic part is large enough so that the hydrophilic nucleus makes no effect as a differentiation group and waxes interact with 3c as a usual paraffin. Thus, results showed that the alkyl chain of the synthesized esters interacts directly with the waxes and chain size is important on inhibition effectiveness.

On the studied crude oil, compound 3b was the most efficient, because the concentration of 200 ppm showed the largest reduction of WAT. Moreover, naphthoquinone may be used as an important polar core to cause differentiations on wax crystals.

A quantitative comparison can be obtained when deposited wax percentages are analyzed. Values can be estimated based on the thermodynamic models developed by Coutinho and Ruffier-Méray. Data of crystalized percentages corroborate those obtained by DSC showing compound 3b is remarkably effective on inhibition, exhibiting a reduction of approximately 1.5% on precipitated paraffin.

The thermograms obtained for ester 3b at different concentrations are shown in Figure 1. The exothermic peak shift to lower temperatures at concentrations of 100 and 200 ppm can be clearly seen. The anomalous behavior at 300 ppm can, in principle, be attributed to a probable nucleation induction in wax. However, no change in the
thermogram profile was observed, which can reveal at least that, at first, there was no selection of paraffins by the inhibitor.

![Thermogram profile](image)

**Figure 1.** Thermogram of ester 3b with different concentrations.

### Conclusions

A new, simple and practical methodology for the Steglich reaction of juglone with long-chain fatty acids employing CeCl$_3$.7H$_2$O as a catalyst was developed on this work, allowing the synthesis of lauric, palmitic and stearic esters in only one step with considerably higher yields, compared to previous methodologies using the same substrate. Simulations showed that the cerium cocatalyst acts rather on the anhydride formed in situ, increasing electrophilicity of intermediate.

Among the synthesized products, compound 3b presented the best effectiveness on WAT reduction, enabling a decrease of 4 °C on WAT and 1.5% of precipitated wax mass. It could be a promising compound for a new class of non-polymeric inhibitors.

### Experimental

#### Materials

All chemicals are commercially available (Sigma-Aldrich) and were used as received: juglone (97%), lauric acid (99.5%), palmitic acid (99.5%), stearic acid (99.5%), N,N'-dicyclohexylcarbodiimide (DCC) (98%), N,N-dimethylaminopyridine (DMAP) (98%), cerium chloride heptahydrate (99%). All solvents used were purchased from Sigma-Aldrich with 98.5% purity (minimum) and with no previous treatment.

#### Methods

$^1$H and $^{13}$C NMR spectra were recorded on a Varian 400 MHz spectrometer in CDCl$_3$. All chemical shifts (δ) are in parts per million (ppm) referred to tetramethylsilane (TMS). IR spectra were measured on an FTLA2000-102 ABB BOMEM spectrophotometer with anhydrous KBr. Melting points were recorded on a FISATOM430 D and are uncorrected.

#### Synthesis of juglone long-chain esters

**General procedure**

In a 50 mL round flask equipped with magnetic stirring, carboxylic acid 2b (2 mmol), DCC (5 mmol) and DMAP (0.4 mmol) were added with 10 mL of THF. The mixture was kept under vigorous stirring for 30 min. Then, a solution of juglone 1 (1 mmol) and CeCl$_3$.7H$_2$O (0.2 mmol) in 10 mL of THF was added dropwise and the reaction was stirred for 24 h. After completion, the solvent was evaporated under reduced pressure and the crude product was solubilized in hexane. The organic layer was washed with brine, dried with Na$_2$SO$_4$ and the solvent was removed in vacuum. The formed solid was purified by column chromatography. Elution with hexane/ethyl acetate (95:5) afforded pure product 3b.

5-O-dodecanoyloxy-1,4-naphthoquinone (3a)

The compound was obtained from the general procedure as a yellow solid with 50% of yield; m.p. 71-74 °C; IR (KBr) $\nu_{\text{max}}$/cm$^{-1}$ 3322, 2923, 2850, 1761, 1662, 1141, 787; $^1$H NMR (400 MHz, CDCl$_3$) δ 0.88 (t, 3H, J 6.9 Hz, CH$_3$), 1.27 (sl, 18H, CH$_2$), 1.82 (q, 2H, J 7.5 Hz, CH$_2$), 2.74 (t, 2H, J 7.5 Hz, CH$_2$), 6.85 (d, 1H, J 10.3 Hz, H-2), 6.94 (d, 1H, J 10.3 Hz, H-2), 7.38 (dd, 1H, J 1.3, 8.0 Hz, H-2), 7.76 (t, 1H, J 8.0 Hz, H-3), 8.05 (dd, 1H, J 1.3, 8.0 Hz, H-3); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 14.1, 22.7, 24.5, 29.2, 29.3, 29.5, 29.6, 31.9, 33.9, 34.2, 123.4, 124.9, 129.8, 133.5, 134.8, 137.3, 139.9, 149.6, 172.1, 183.6, 184.3.

5-O-hexadecanoyloxy-1,4-naphthoquinone (3b)

The compound was obtained from the general procedure as a yellow solid with 56% of yield (224 mg); m.p. 72-73 °C; IR (KBr) $\nu_{\text{max}}$/cm$^{-1}$ 3345, 2921, 2849, 1761, 1660, 1142, 788; $^1$H NMR (400 MHz, CDCl$_3$) δ 0.88 (t, 3H, J 6.9 Hz, CH$_3$), 1.26 (sl, 26H, CH$_2$), 1.82 (q, 2H, J 7.5 Hz, CH$_2$), 2.74 (t, 2H, J 7.5 Hz, CH$_2$), 6.85 (d, 1H, J 10.3 Hz, H-2), 6.94 (d, 1H, J 10.3 Hz, H-2), 7.38 (dd, 1H, J 1.3,
Wax deposition inhibitor activity

Calorimetric analyses were recorded on a thermal analyzer MDSCQ200 TA Instruments coupled with a DSC Q200 cooling system. All experiments were performed under \( \text{N}_2 \) atmosphere. The heating program consisted of a heating until 80 °C (heating rate 1 °C min\(^{-1} \)) followed by an isotherm at same temperature for 15 min. Then, the system was cooled to −20 °C (cooling rate 0.8 °C min\(^{-1} \)) followed by another isotherm for 15 min. Then, the system was cooled to −20 °C (cooling rate 0.8 °C min\(^{-1} \)) followed by another isotherm for 15 min.

Values presented for W\( \text{AT} \) were obtained by a simple average of two experiments.

### Supplementary Information

Supplementary information (spectral data for IR, \(^1\)H and \(^{13}\)C NMR of the synthesized compounds) is available free of charge at http://jbc.ssbq.org.br as PDF file.

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### References

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