

## Synthesis of $\alpha$ - and $\beta$ -Lapachone Derivatives from Hetero Diels-Alder Trapping of Alkyl and Aryl *o*-Quinone Methides

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Foram sintetizados, em um único pote reacional, alguns derivados da  $\alpha$ - e  $\beta$ -lapachonas a partir de reação de hetero Diels-Alder, em etanol aquoso, entre estirenos substituídos (como dienófilos) e *o*-quinonas metídeos (*o*-QMs) metilênicas e arílicas geradas por condensação de Knoevenagel da 2-hidróxi-1,4-naftoquinona com formaldeído e aldeídos aromáticos.

Methylene and aryl *o*-quinone methides (*o*-QMs) generated by Knoevenagel condensation of 2-hydroxy-1,4-naphthoquinone with formaldehyde and arylaldehydes, undergo facile hetero Diels-Alder reaction with some substituted styrenes (as dienophiles) in aqueous ethanol media providing derivatives of  $\alpha$ - and  $\beta$ -lapachone.

**Keywords:** *o*-Quinone methides, Knoevenagel condensation, Hetero Diels-Alder, Lapachones

### Introduction

Quinones have been extensively studied for antitumoral,<sup>1</sup> molluscicidal,<sup>2</sup> parasiticidal,<sup>3</sup> leishmanicidal,<sup>4</sup> anti-inflammatory,<sup>5</sup> fungicidal,<sup>6</sup> antimicrobial<sup>7</sup> and trypanocidal<sup>8</sup> activities. Reports point out that the biological profiles of these molecules are centralized on their *ortho* or *para*-quinonoid moiety that generally accepts one and/or two electrons (redox cycling) to form the corresponding radical anion or dianion species *in situ*.<sup>9</sup> Thus, the semi-quinone radicals accelerate intracellular hypoxic conditions by producing superoxide anion.<sup>10,11</sup> Due to this mechanism, quinones may present cytotoxicity to mammalian cells, possibly by affecting enzymes such as topoisomerases, a group of enzymes that are critical for DNA replication in cells.<sup>12</sup>

The data described in the literature so far clearly show that the naphthoquinone frameworks have important significance for the development of new substances with promising biological activities.<sup>13,14</sup> Therefore, new synthetic methodologies that could lead to the preparation of these compounds are very important.<sup>15</sup>

*o*-Quinone methides (*o*-QMs) are useful reactive intermediates in organic synthesis (Scheme 1)<sup>16</sup> and involved in a large number of chemical reactions and biological processes, such as enzyme inhibition, reaction with phosphodiester, DNA alkylation and cross-linking.<sup>17</sup> Since *o*-QMs are usually unstable intermediates, they must be generated *in situ* by processes that can involve photolysis of *o*-, *m*- and *p*-hydroxybenzyl alcohols<sup>18</sup>, thermal reactions<sup>19,20</sup>, and anionic triggering reactions.<sup>21</sup> However, some *o*-QMs may be sufficiently stable and can be isolated, depending on their structural arrangement.<sup>22</sup>

Dagliesh was the first one to suggest that an *o*-QM was a possible intermediate in an organic reaction.<sup>23</sup> However, the first example of generation and use of an *o*-QM in intramolecular hetero Diels-Alder reaction was reported by Brougidou and Christol.<sup>24,25</sup> Following this discovery many studies demonstrated that these hetero-diene moieties are suitable for [4 + 2] cycloadditions with a wide range of dienophiles.

Our group became interested in the chemistry of these intermediates in 1982<sup>26</sup> when we reported a novel preparation of the tetracyclic  $\alpha$ - and  $\beta$ -pyranonaphthoquinones (**3** and **4**) in 70% yield by the reaction of citronellal (**2**)<sup>27</sup> with lawsone (**1**). The *o*-QM intermediate was generated

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*in situ*, (Scheme 1, Eq. 1) by a Knoevenagel reaction that upon hetero-Diels-Alder cycloaddition formed the pyranonaphthoquinones **3** and **4**.

Recently, Nair *et al.* reported in a series of papers the study of the reactivity and use of several *o*-QMs<sup>28,29</sup> in intermolecular reaction Diels-Alder reaction. This three-component reaction (Scheme, Eq. 2) overcame the limitation regarding the use of aldehydes having the dienophiles in the same structure and it was used for the synthesis of several derivatives of  $\alpha$ - and  $\beta$ -lapachone and other heterocyclic compounds. Both intra- and intermolecular hetero Diels-Alder reactions shown in Scheme 1 result in the 1,4-naphthoquinone as the major isomer. This methodology still attracts research groups interested in the synthesis of naphthoquinone derivatives.<sup>30</sup>

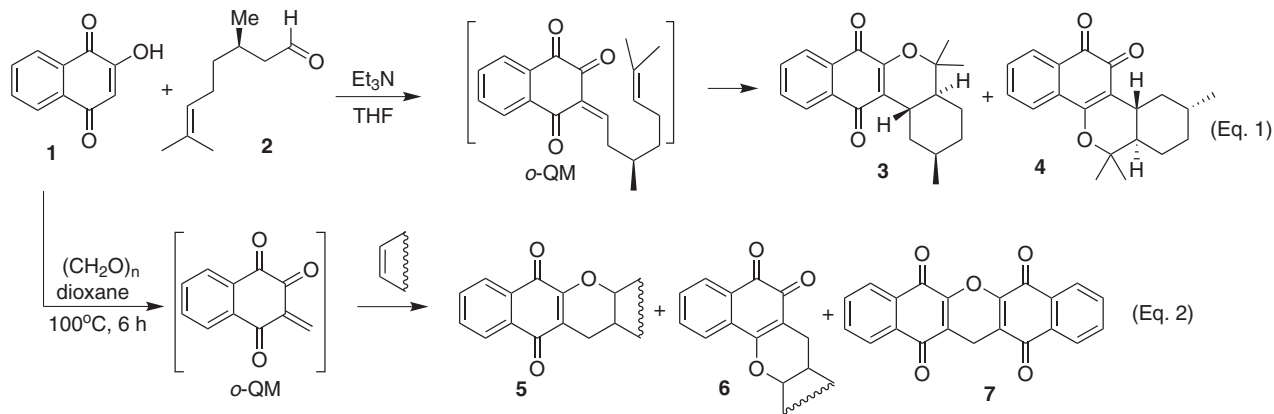
Despite its scope, this three-components reaction described in Eq.2 (Scheme 1) it still limited to the use of formaldehyde. Other aromatic aldehydes do not react under

these conditions and most of them produce xanthenes (e.g **7**, in Scheme 1) instead of Diels-Alder adducts.

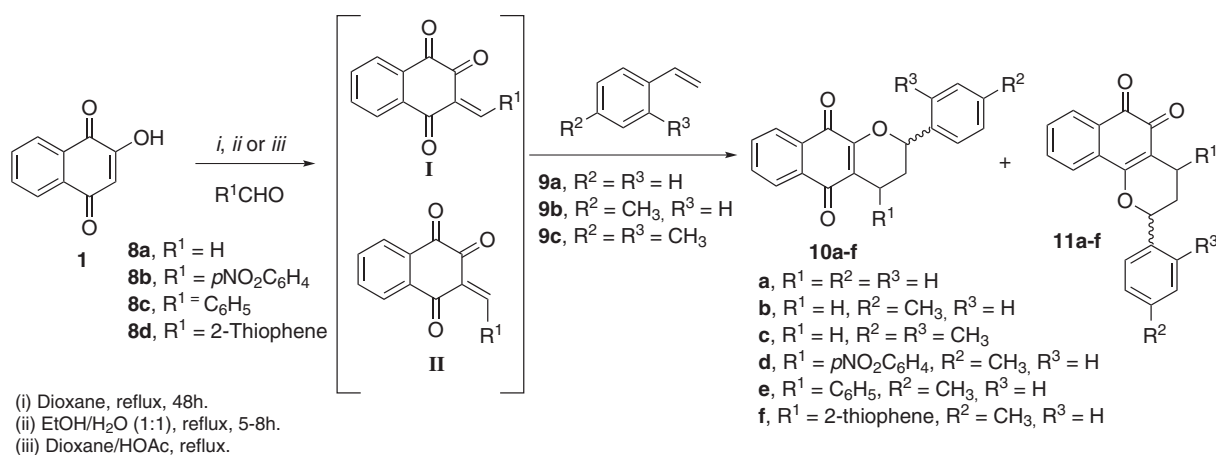
In this communication we report our finds on the preparation of  $\alpha$ - and  $\beta$ -lapachone derivatives *via* methylene and aryl *o*-quinone methides (*o*-QMs) generated *in situ* by Knoevenagel condensation of 2-hydroxy-1,4-naphthoquinone (**1**) with formaldehyde and arylaldehydes (**8**) followed by hetero Diels-Alder reaction with substituted styrenes (**9**) in aqueous ethanol media (Scheme 2).

## Results and Discussion

The reaction of lawsone (**1**), formaldehyde (**8a**) and substituted styrenes (**9**) in dioxane worked as expected according to the protocol developed by Nair *et al.*<sup>28</sup> (entries 1-3, Table 1). Despite the good performance achieved in previous reactions, it did not work with aromatic aldehydes even for periods exceeding 48 h of reflux (entries 4-6, Table 1).



**Scheme 1.** *o*-QMs as hetero-dienes for constructing chromanes substructures.



**Scheme 2.** Knoevenagel/hetero Diels-Alder reactions of **8** with aldehydes and styrenes in aqueous ethanol media.

**Table 1.** Hetero Diels–Alder reactions in dioxane media

Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Yield %	Ratio $\alpha/\beta^a$
1	H	H	H	80	4.3
2	H	CH <sub>3</sub>	H	85	4.7
3	H	CH <sub>3</sub>	Me	97	7.1
4	4-NO <sub>2</sub> Ph	CH <sub>3</sub>	H	No reaction	-
5	2-thiophene	CH <sub>3</sub>	H	No reaction	-
6	Ph	CH <sub>3</sub>	H	No reaction	-

<sup>a</sup>The ratio  $\alpha/\beta$  were determined by <sup>1</sup>H-NMR. The reactions were achieved in 48 hs.

Aiming to improve the scope of this reaction, and thus obtain various derivatives of lapachones, we decided to investigate the effect of the solvent, having in mind that the Diels–Alder reactions are accelerated by acids. Several reaction conditions were investigated, however best results were achieved by the reaction in ethanol/water in the proportion of 1:1 under reflux. The results are summarized in Table 2.

Comparing the results described in Table 1 (entries 1-3) with those of Table 2 (entries 1-3), we can observe that the mixture of solvents ethanol/water had effect on the yields, reaction time and the ratio between isomers  $\alpha$  and  $\beta$ . The reactions were faster and the yields improved as well the proportion of  $\beta$  isomer.

The effect of ethanol/water solvent mixture was more significant in the reactions with aromatic aldehydes (**8b-d**). The reactions that had not worked previously, in this new condition produced the disubstituted naphthoquinones  $\alpha$  (*syn:anti*, **10d-f**) and  $\beta$  (*syn:anti*, **11d-f**) in good yields (entries 3-6, Table 2). A very important point that should

be emphasized was the high proportion of  $\beta$ -isomer (**11d-f**) under these new conditions.

Each of these reactions produced a mixture of  $\alpha$  and  $\beta$  isomers that were composed of *syn* and *anti* diastereoisomers. In most cases the proportion of the *anti* isomer was higher than the *syn* (**10d-f**). The four compounds of these mixtures were separated by flash column chromatography and their structures were determined by 1D and 2D NMR techniques and by ESI-TOF mass spectrometry. The  $\alpha$  and  $\beta$ -isomers (**10d-f** and **11d-f**) could be distinguished by the hydrogens of the aromatic region because of a more symmetrical pattern of the  $\alpha$ - isomers in comparison with that of the  $\beta$  isomer. The diastereoisomers *syn* and *anti* were distinguished by the coupling constants of hydrogens H-3 and H-4 of the pyran rings that showed  $J$  equal to 2.4/5.9 and 11.0/7.1 Hz ( $J_{3a,4}/J_{3b,4}$ ) for the *syn* and *anti* isomers, respectively and hydrogens H-3 and H-2 with coupling constants values of 2.4/12.0 Hz ( $J_{3a,2}/J_{3b,2}$ ) for *syn* isomers and 2.2 and 11.2 Hz ( $J_{3a,2}/J_{3b,2}$ ) for *anti* isomers.<sup>32</sup>

Recently, Peng and co-workers<sup>33</sup> performed DFT calculations for the reaction between unsubstituted *o*-QM and several dienophiles, including styrene. The proposed molecular mechanisms for these reactions were postulated to be asynchronicity concert cycloaddition mechanism. The activation energies for the *ortho* attack modes is lower than *meta* ones. Their calculations also show that the effect of solvent decreases the activation energy and increases the asynchronicity. Regarding the regioselectivity, our reactions are in complete agreement with a [4+2] cycloaddition of the *o*-QM with the styrene in asynchronous fashion by zwitterion-like transition

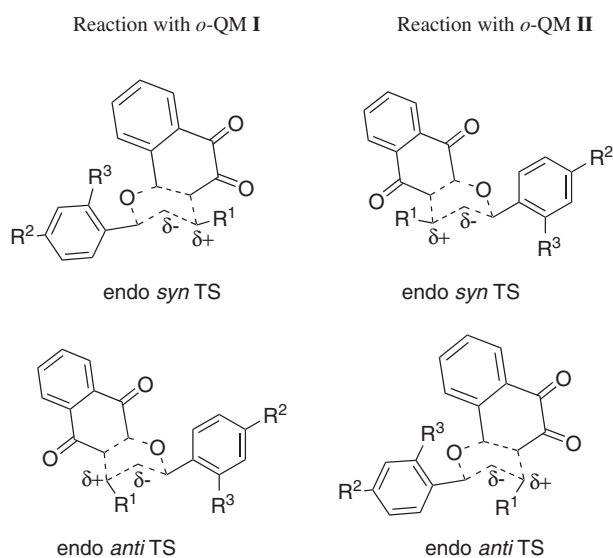
**Table 2.** Hetero Diels–Alder reactions in aqueous ethanol media or dioxane

Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Conditions	Time (h)	Yield %	Ratio $\alpha/\beta$ ( <b>10:11</b> ) <sup>a</sup>	$\alpha$ ( <i>syn:anti</i> )	$\beta$ ( <i>syn:anti</i> )
1	H	H	H	EtOH/H <sub>2</sub> O (1:1)	6	94	3.1	-	-
2	H	CH <sub>3</sub>	H	EtOH/H <sub>2</sub> O (1:1)	6	95	3.8	-	-
3	H	CH <sub>3</sub>	Me	EtOH/H <sub>2</sub> O (1:1)	6	97	4.7	-	-
4	4-NO <sub>2</sub> Ph	CH <sub>3</sub>	H	EtOH/H <sub>2</sub> O (1:1)	5	50	1.4	37:63	18:82
5	2-thiophene	CH <sub>3</sub>	H	EtOH/H <sub>2</sub> O (1:1)	8	60	0.8	54:46	0:100
6	Ph	CH <sub>3</sub>	H	EtOH/H <sub>2</sub> O (1:1)	8	52	0.6	20:80	12:88
7	H	H	H	Dioxane/ HOAc	4	96	2.2	-	-
8	4-NO <sub>2</sub> Ph	CH <sub>3</sub>	H	Dioxane/ HOAc	5	55	1.1	35:65	17:83

<sup>a</sup>The ratio  $\alpha/\beta$  and the diastereoisomers *syn* and *anti* were determined by <sup>1</sup>H-NMR.

state. Xu and co-workers<sup>30</sup> generated in situ the *o*-QMs **I** and **II** (Scheme 2) and reacted then with several silyl enol ethers obtaining regioselectively  $\alpha$ -lapachone derivatives with *anti* stereoselectivity in moderate to high yield. The regioselectivity was rationalized by considering favorable pathway to a zwitterion-like transition state of lower energy between the reactants. DFT calculation indicated that *o*-QM **I** has lower LUMO energy than **II**. However, no rationalization was attempted by the author to explain the *anti* stereoselectivity.

Since the intermediate **I** is the most stable one, we can speculated that it forms preferentially the  $\alpha$ - and  $\beta$ -*anti* adducts with the proper regiochemistry by a chair-like *endo* transition state as indicated in Figure 1.



**Figure 1.** Proposed transition states formed by *o*-QM **I** or **II** with **9a-c**.

The acceleration of the Diels-Alder reactions by aqueous media is well known.<sup>34</sup> However, the acidity of the mixture ethanol:water is more relevant for success of the reactions. In an attempt to investigate this hypothesis, we decided to carry out the reactions of the compound **1** with aldehydes and styrenes in dioxane, containing catalytic amount of acetic acid (entries 7 and 8, Table 2). The comparison between the experiments of entries 1 and 7 of Table 2 clearly show the effect of the acidic media and increasing the proportion of  $\beta$ -isomers. In these experiments formation of the by-product benzoxanthene (type **7**) was negligible.

## Conclusions

In summary, the methodology described by Nair *et al.* has been improved, resulting in  $\beta$ -pyranonaphthoquinones more selectively and in better yields and lower reaction

time. Additionally, with this methodology it was possible to use any type of aldehyde, and not only formaldehyde.

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## Supplementary Information

Supplementary data are available free of charge at <http://jbcbs.org.br>, as PDF file.

## References

- Lee, J. H.; Cheong, J. H.; Park, Y. M.; Choi, Y. H.; *Pharmacolog. Res.* **2005**, *51*, 553; Skibo, E. B.; Xing, C.; Dorr, R. T.; *J. Med. Chem.* **2001**, *44*, 3545.
- dos Santos, A. F.; Ferraz, P. A. L.; de Abreu, F. C.; Chiari, E.; Goulart, M. O. F.; Sant'Ana, A. E. G.; *Planta Med.* **2001**, *67*, 92; Barbosa, T. P.; Camara, C. A.; Silva, T. M. S.; Martins, R. M.; Pinto, A. C.; Vargas, M. D.; *Bioorg. Med. Chem.* **2005**, *13*, 6464.
- Ferreira, V. F.; Jorqueira, A.; Souza, A. M. T.; Da Silva, M. N.; de Souza, M. C. B. V.; Gouvêa, R. M.; Rodrigues, C. R.; Pinto, A. V.; Castro, H. C.; Santos, D. O.; Araújo, H. P.; Bourguignon, S. C.; *Bioorg. Med. Chem.* **2006**, *14*, 5459; Jorqueira, A.; Gouvêa, R. M.; Ferreira, V. F.; da Silva, M. N.; de Souza, M. C. B. V.; Zuma, A. A.; Cavalcanti, D. F. B.; Araújo, H. P.; Bourguignon, S. C.; *Parasitol. Res.* **2006**, *99*, 429; Silva-Jr, E. N.; Menna-Barreto, R. F. S.; Pinto, M. C. F. R.; Silva, R. S. F.; Teixeira, D. V.; de Souza, M. C. B. V.; Simone, C. A.; de Castro, S. L.; Ferreira, V. F.; Pinto, A. V.; *Eur. J. Med. Chem.* **2008**, *43*, 1774.
- Teixeira, M. J.; de Almeida, Y. M.; Viana, J. R.; Holanda, J. G.; Rodrigues, T. P.; Prata, J. R. C.; Coelho, I. V. B.; Rao, V. S.; Pompeu, M. M. L.; *Phytother. Res.* **2001**, *15*, 44.
- de Almeida, E. R.; Filho, A. A. S.; dos Santos E. R.; Lopes C. A. C.; *J. Ethnopharmacol.* **1990**, *29*, 239.
- Gafner, S.; Wolfender, J. L.; Nianga, M.; Stoeckli-Evans, H.; Hostettmann, K.; *Phytochemistry* **1996**, *42*, 1315.
- Tabata, M.; Tsukada, M.; Fukui, H.; *Planta Med.* **1982**, *44*, 234.
- Salas, C.; Tapia, R. A.; Ciudad, K.; Armstrong, V.; Orellana, M.; Kemmerling, U.; Ferreira, J.; Maya, J. D.; Morello, A.; *Bioorg. Med. Chem.* **2008**, *16*, 668; Dubin, M.; Villamil, S. H. F.; Stoppani, A. O. M.; *Medicina-Buenos Aires* **2001**, *61*, 343; Pinto, C. N.; Dantas, A. P.; de Moura, K. C. G.; Emery, F. S.; Polequevitch, P. F.; Pinto, M. D.; de-Castro, S. L.; Pinto, A. V.; *Arzneim. Forsch.* **2000**, *50*, 1120.
- Salmon-Chemin, L.; Buisine, E.; Yardley, V.; Kohler, S.; Debreu, M.-A.; Landry, V.; Sergheraert, C.; Croft, S. L.; Krauth-Siegel, R. L.; Davioud-Charvet, E.; *J. Med. Chem.* **2001**, *44*, 548.

10. Santos, E. V. M.; Carneiro, J. W. M.; Ferreira, V. F.; *Bioorg. Med. Chem.* **2004**, *12*, 87.
11. Hickman, J. A.; *Curr. Opin. Genet. Dev.* **2002**, *12*, 67.
12. Esteves-Souza, A.; Figueiredo, D. V.; Esteves, A.; Camara, C. A.; Vargas, M. D.; Pinto, A. C.; Echevarria, A.; *Braz. J. Med. Biol. Res.* **2007**, *40*, 1399.
13. Monks, T. J., Jones, D. C.; *Curr. Drug Metabolism* **2002**, *3*, 425.
14. Silva, M. N.; Ferreira, V. F.; de Souza, M. C. B. V.; *Quim. Nova* **2003**, *26*, 407.
15. da Silva A. R.; da Silva, A. M.; Ferreira, A. B. B.; Bernardes, B. O.; da Costa, R. L.; *J. Braz. Chem. Soc.* **2008**, *19*, 1230; Silva, R. S. E.; de Amorim, M. B.; Pinto, M. D. C. F. R.; Emery, F. S.; Goulart, M. O. F.; Pinto, A. V.; *J. Braz. Chem. Soc.* **2007**, *18*, 759; Uliana, M. P.; Vieira, Y. W.; Donatoni, M. C.; Corrêa, A. G.; Brocksom, U.; Brocksom, T. J.; *J. Braz. Chem. Soc.* **2008**, *19*, 1484; Vieira, Y. W.; Nakamura, J.; Finelli, F. G.; Brocksom, U.; Brocksom, T. J.; *J. Braz. Chem. Soc.* **2007**, *18*, 448.
16. Van De Walters, R. W.; Pettus, T. R. R.; *Tetrahedron* **2002**, *58*, 5367.
17. Wang, P.; Song, Y.; Zhang, L. X.; He, H. P.; Zhou, X.; *Curr. Med. Chem.* **2005**, *12*, 2893.
18. Brousmiche, D. W.; Wan, P.; *J. Photochem. Photobiol., A* **2002**, *149*, 71.
19. Dorrestijn, E.; Pugin, R.; Nogales, M. V. C.; Mulder, P.; *J. Org. Chem.* **1997**, *62*, 4804.
20. Wojciechowski, K.; Dolatowska, K.; *Tetrahedron* **2005**, *61*, 8419.
21. van de Water, R. W.; Magdziak D. J.; Chau J. N.; Pettus, T. R. R.; *J. Am. Chem. Soc.* **2000**, *122*, 6502; Jones, R. M.; van de Water, R. W.; Lindsey, C. C.; Hoarau, C.; Ung, T.; Pettus, T. R. R.; *J. Org. Chem.* **2001**, *66*, 3435; Kiselyov, A. S.; *Tetrahedron Lett.* **2001**, *42*, 3053.
22. da Silva, M. N.; Ferreira, S. B.; Jorqueira, A.; de Souza, M. C. B. V.; Pinto, A. V.; Kaiser, C. R.; Ferreira, V. F.; *Tetrahedron Lett.* **2007**, *48*, 6171.
23. Dalglish, C. E.; *J. Am. Chem. Soc.* **1949**, *71*, 1697.
24. Brougidou, J.; Christol, H.; *C. R. Hebd. Acad. Sci.* **1963**, *257*, 3149.
25. Brougidou, J., Christol, H.; *C. R. Hebd. Acad. Sci.* **1963**, *257*, 3323.
26. Ferreira, V. F.; Coutada, L. C.; Pinto M. C. F. R.; Pinto, A. V.; *Synth. Commun.* **1982**, *12*, 195.
27. Ferreira, V. F.; Pinto, A. V.; Coutada, L. C. M.; *An. Acad. Brasil. Cienc.* **1980**, *52*, 477.
28. Nair, V.; Mathew, B.; Rath, N. P.; Vairamani, M.; Prabhakar, S.; *Tetrahedron* **2001**, *57*, 8349.
29. Nair, V.; Jayan, C. N.; Radhakrishnan, K. V.; Anilkumar, G.; Rath, N. P.; *Tetrahedron* **2001**, *57*, 5807; Nair, V.; Treesa, P. M.; *Tetrahedron Lett.* **2001**, *42*, 4549; Nair, V.; Treesa, P. M.; Jayan, C. N.; Rath, N. P.; Vairamani, M.; Prabhakar, S.; *Tetrahedron* **2001**, *57*, 7711; Nair, V.; Menon, R. S.; Vinod, A. U.; Viji, S.; *Tetrahedron Lett.* **2002**, *43*, 2293.
30. Peng, D. -Q.; Liu, Y.; Lu, Z. -F.; Shen, Y. -M.; Xu, J. -H.; *Synthesis* **2008**, 1182.
31. Teimouri, M. B.; Khavasi, H. R.; *Tetrahedron* **2007**, *63*, 10269.
32. General Procedure for preparing **10a-f** and **11a-f**. To a round-bottom flask equipped with a magnetic stirring bar was added dissolved lawsone (1 mmol) with water (10 mL) and ethanol (10 mL). Then, the appropriate aldehyde (8 mmols for paraformaldehyde or 3 mmols for arylaldehydes) was added, followed by dropwise addition of the substituted styrenes (3 mmol). The reaction mixture was stirred under reflux until consumption of the starting material (5-8 h). The ethanol was removed under reduced pressure and ethyl acetate (50 mL) was added to the residue and the mixture was washed with saturated aqueous solution of sodium bicarbonate (2  $\times$  20 mL). The organic phase was washed with water (2  $\times$  50 mL), dried over anhydrous sodium sulphate, filtered and concentrated under vacuum. The residual crude product was purified by column chromatography on silica gel using gradient mixture of hexane-ethyl acetate.
33. Wang, H.; Wang, Y.; Han, K. -L.; Peng, X. -J.; *J. Org. Chem.* **2005**, *70*, 4910.
34. Wijnen, J. W.; Engberts, J. B. F. N.; *J. Org. Chem.* **1997**, *62*, 2039; Deshpande, S. S.; Kumar, A.; *Tetrahedron*, **2005**, *61*, 8025; Sarma, D.; Pawar, S. S.; Deshpande, S. S.; Kumar, A. *Tetrahedron Lett.* **2006**, *47*, 3957.
35. Chen, Y.; Wu, S.; Tu, S.; Li, C.; Shi, F.; *J. Heterocycl. Chem.* **2008**, *45*, 931.

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