

Synthesis of new carbonyl and fluoroalkyl *o*-quinone methides from β -lapachone

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Received 20 April 2007; revised 23 June 2007; accepted 26 June 2007

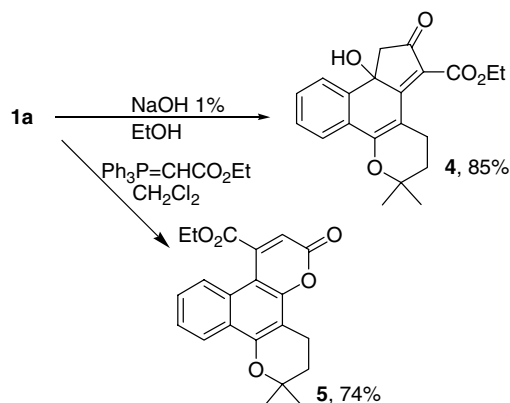
Available online 4 July 2007

Abstract—The synthesis of new carbonyl and fluoroalkyl *o*-quinone methides from β -lapachone is reported.
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o-Quinones (*o*-Qs) and *o*-quinone methides (*o*-QMs) are related sub-structural moieties present in several bioactive compounds with high interest due to several related biological activities. For example, quinones have been studied for antitumor,¹ molluscicidal,² leishmanicidal,³ anti-inflammatory,⁴ antifungic,⁵ and trypanocidal⁶ activities. This group generally accepts one and/or two electrons (redox cycling) to form the corresponding radical anion or dianion species in situ. In such a way, the semi-quinone radicals accelerate the intracellular hypoxic conditions by producing a superoxide anion.⁷ Quinone methides, on the other hand, are reactive intermediates involved in a large number of chemical reactions and biological processes such as enzyme inhibition, reaction with phosphodiester, DNA alkylation, and cross-linking.⁸ Their electrophilicity towards amines, thiols, water, amino acids and peptides has also been used for interactions with DNA bases.⁹ Several important clinical anti-cancer drugs (e.g., cisplatin, psoralens, and mitomycin C) are known to induce DNA ISC formation, which can disrupt cell maintenance and replication by a mechanism that involve *o*-QMs intermediates. Since *o*-QMs are unstable intermediates, they must be generated in situ by processes that involve photolysis of *o*-, *m*- and *p*-hydroxybenzyl alcohols,¹⁰ thermal reactions,¹¹ and anionic triggering reactions.¹²

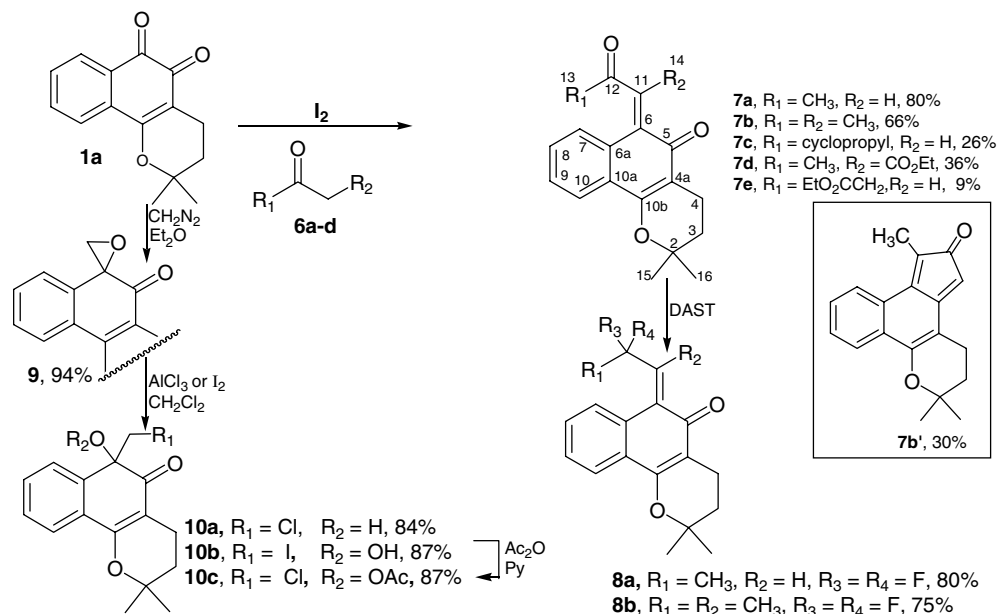
β -Lapachone (**1a**) is an *o*-naphthoquinone that can be isolated from plant extracts of *Tabebuia avellanedae*. It had been intensely investigated for clinical use as trypanocidal, HIV-1 replication¹³ suppression in both acute and chronic infection and, topoisomerases inhibition that has potential clinical utility for human leukemia and prostate cancer chemotherapy.¹⁴

Since the transformation of *o*-quinones into *o*-quinone methides adds new biological possibilities, it seems that an interesting starting point is to transform bioactive naphthoquinones, such as **1a**, into new lead compounds. Two recent studies have been carried out (Scheme 1).



Scheme 1. Recent reports involving the transformations of **1a**.

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Scheme 2. *o*-QMs and fluorinated *o*-QMs obtained from β -lapachone (**1a**).

Pinto and co-workers¹⁵ studied the aldol condensation using NaOH 1%/EtOH isolating a dihydro-cyclopentanone (**4**) adduct in 85% yield. It is worthy to note that compound **4** upon acid treatment led to cyclopentanone. Nicolaides and co-workers¹⁶ have studied the Wittig reactions of *o*-quinones, as **1a** and derivatives, with alkyl-carbonyl-methylene (triphenyl)-phosphoranes.

In this Letter, we present our efforts on the preparation of stable *o*-QMs and fluorinated *o*-QMs from β -lapachone (**1a**), as well as three halogenated derivatives (**8a-c**), which might be a source of non-substituted *o*-QM of **1a**. In order to perform these transformations chemoselective reactions between β -lapachone (**1a**) with several ketones catalyzed by iodine were done to produce *o*-QMs **7a-e**, in moderate to good yields. *o*-QMs **7a-b** was also reacted with DAST to produce fluorinated *o*-QMs **10a-b**, as outlined in Scheme 2.

The preparation of *o*-QMs **7a-e** was carried out in one step by aldol condensation reactions between β -lapachone **1a** with ketones **6a-d** at room temperature. The reaction of ketones **6a** and **6c** with **1a** lead exclusively to products **7a** and **7c** with the configuration *E* in exocyclic double bond. The reaction of ketone **6b** should furnish two *o*-QMs products, but only *o*-QM **7b** with the configuration *E* was isolated, since the *Z* isomer underwent a second aldol condensation producing cyclopentanone **7b'**. The reaction with ketone **6d** gave a complex mixture, from which was possible to isolate the *o*-QMs **7d** and **7d'** in low yields.

The chemoselectivities found in the reactions of **1a** were not surprising, since there are several reports in the literature indicating that the carbonyl nearest to the aromatic ring is the more reactive.¹⁷ The formation mainly of the *E* diastereoisomer products observed in these reactions was governed by steric effects.¹⁸

The confirmation of such frameworks behavior was done by ¹H and ¹³C NMR including 2D NMR techniques as COSY, HSQC, HMBC and NOESY. For example, in **7a** it is possible to clearly confirm that the exocyclic olefin was formed at the C-6 carbonyl due to correlations between H-13 and H-7 in the NOESY spectrum. This result also confirms that its configuration can be securely assigned as *E*.

Treatment of *o*-QMs **7a-b** with DAST in dry dichloromethane at room temperature for 24 h gave the alkyl-fluorinated *o*-QMs **8a-b** in 80% and 75% yields, respectively. The NOESY spectra in the same way as above, show the H-13 and H-7 correlations and confirm the *E* configuration for these compounds.

Since non-substituted *o*-QMs were never isolated, we also studied an alternative route that could lead to unsubstituted *o*-QMs of **1a**. As shown in Scheme 2, the synthesis of **10a-b** was carried out in two steps. The first involved the preparation of lapachone-oxyran derivative **9**, which was obtained in high yield from the reaction of **1a** with diazomethane in ether.¹⁹ In the second step oxyran **9** was reacted with $AlCl_3$ and iodine in DCM at room temperature. Both these Lewis acids catalyzed the opening of the oxyran ring furnishing substances **10a-b** in high yield. Additionally, compound **10a** was transformed into the acetate derivative **10c** to produce a compound with a better leaving group for the generation of *o*-QM. However, all the attempts to generate and isolate *o*-QMs from **10a-c** were unsuccessful.

In summary, a novel method for the synthesis of stable *o*-quinone methides from β -lapachone (**1a**) is described. The aldol condensation under iodine-catalyzed process forming the *o*-QMs **7a-e** occurs chemoselectively and diastereoselectively at the 6-carbonyl groups. Two of these *o*-QMs were transformed into alkyl-fluorinated

o-QMs **8a–b**, which turns also to be stable. Additionally, three new compounds (**10a–c**) that can generate in situ *o*-QMs²³ were prepared from the oxyran **7** in high yields. To the best of our knowledge, the preparation of the presented *o*-QMs represents the first example of the chemoselective and diastereoselective formation of stable *o*-quinone methides from β -lapachone (**1a**). Full experimental details and ¹H, ¹³C NMR spectra data are available in the supporting informations. See [Supplementary data](#).

Acknowledgements

This work was supported by CNPQ (National Council of Research of Brazil), CAPES, FINEP, FAPERJ, UFRJ and UFF.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2007.06.145](https://doi.org/10.1016/j.tetlet.2007.06.145).

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