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Three-component reductive alkylation of 2-hydroxy-1,4-naphthoquinones with lactols

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ABSTRACT

Lactols **II**, obtained by DIBAL reduction of their corresponding lactones **I**, in equilibrium with their hydroxyaldehyde tautomers **III** were used in a three-component reductive alkylation with 2-hydroxy-1,4-naphthoquinone to give a series of 3-alkylated 2-hydroxy-1,4-naphthoquinone derivatives **IV**.

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We recently reported the synthesis of monofluorinated 3-alkyl-2-hydroxy-1,4-naphthoquinone **1** by the L-proline-catalyzed three-component reductive alkylation (TCRA) of 2-hydroxy-1,4-naphthoquinone (**2**) with chiral aldehyde **3** (Fig. 1).¹ Fluorinated **1**² has been touted as a potential anti-malarial compound that could enhance the species selectivity and metabolic stability of atovaquone and other inhibitors of the cytochrome *bc*₁ complex of the malaria parasite *Plasmodium falciparum*.³

Following our enantioselective synthesis of **1** and for the purpose of determining its enantiomeric excess in order to support further biological assays, we needed to synthesize the racemic mixture for comparison. We had initially planned to utilize the chemistry already established. However, despite literature precedence for α -methylation of methyl esters,⁴ our attempts to alkylate (LDA or NaHMDS/Mel) the methyl ester **7**¹ failed to provide sufficient quantities of **8** (Scheme 1).

As an alternative, we synthesized the lactone **9** in 70% yield by treating 8-bromooctanoic acid (**4**) with TBAF·3H₂O in *tert*-butanol at 70 °C overnight (Scheme 2). The trace amount of the 8-fluorooctanoic acid side product from this reaction was easily removed by column chromatography. While the tetra-*n*-butyl-ammonium fluoride trihydrate (TBAF·3H₂O)-induced esterification of halo carboxylic acids has been reported in the literature,^{5,6} this is the first time oxonan-2-one (**9**) has been synthesized by this methodology. Furthermore, our new synthesis of **9** is much more efficient

than the literature methods.^{7,8} For example, the synthesis of **9** using *m*-CPBA required extended reaction times⁹ (1–14 days) and were often complicated by the removal of unreacted starting material that has a nearly identical TLC *R*_f and boiling point to the product. Also, other Baeyer–Villiger oxidation procedures⁷ were equally encumbered by isolation and purification problems. With **9** in hand, α -methylation to afford **10** was achieved in 95% yield upon treatment of **9** with lithium diisopropyl amide (LDA) at –78 °C followed by the addition of MeI.¹⁰ Even though 3-methyloxonan-2-one (**10**) is a known compound, a recent article reporting on its thermodynamic properties did not provide details for its preparation.¹¹ Next, partial DIBAL reduction of **10** gave hydroxyaldehyde **11** in equilibrium with a small amount of its lactol tautomer **12**.

Subsequent L-proline-catalyzed three-component reductive alkylation of **2** and Hantzsch ester (**5**) gave lawsone derivative **13**, a precursor to **1**, in a yield of 89% (Scheme 3).^{1,12} This reaction mirrors the previously reported aldol reactions employing lactols in equilibrium with their hydroxyaldehydes.^{13,14}

To expand the scope of this reaction, other lactones **14–18** were either obtained from commercial sources or synthesized from their corresponding cycloketones via standard *m*-CPBA oxidation. Methylated lactones were also either commercially available or synthesized via literature procedures (Table 1, entries 4⁷ and 5¹⁵) using LDA or NaHMDS with MeI. The TCRA reaction of DIBAL products from these lactones proceeded smoothly to furnish 2-hydroxy-1,4-naphthoquinones. Representative examples, **19–24**,^{16,17} are summarized in Table 1. In general, DIBAL reduction of small ring lactones (butyro- and valerolactone) (Table 1, entries 1

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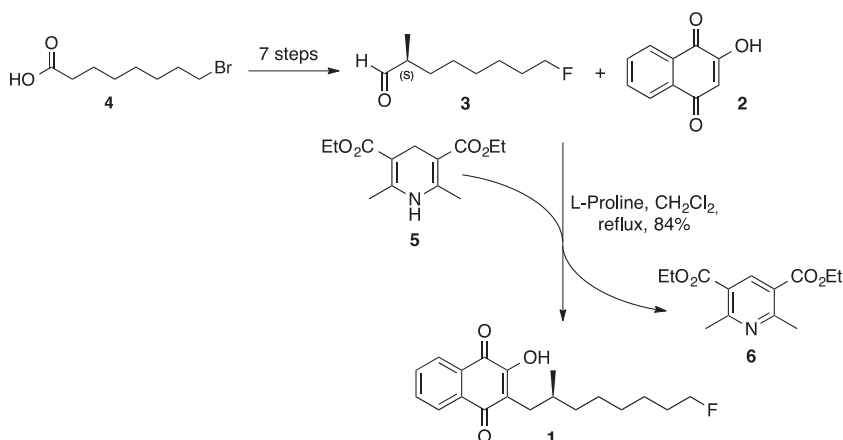
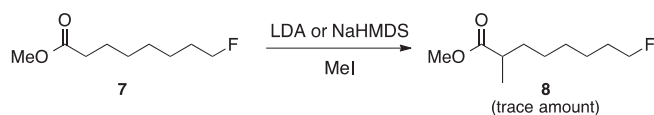


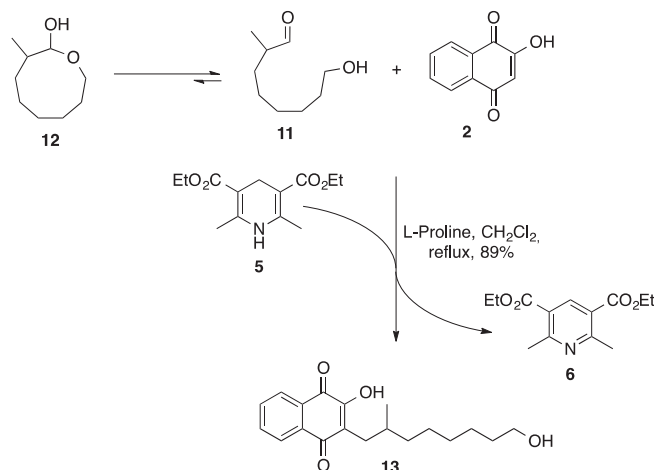
Figure 1. Previous synthesis of monofluorinated 3-alkyl-2-hydroxy-1,4-naphthoquinone **1**.



Scheme 1. Attempted α -methylation of fluoro methyl ester **7**.

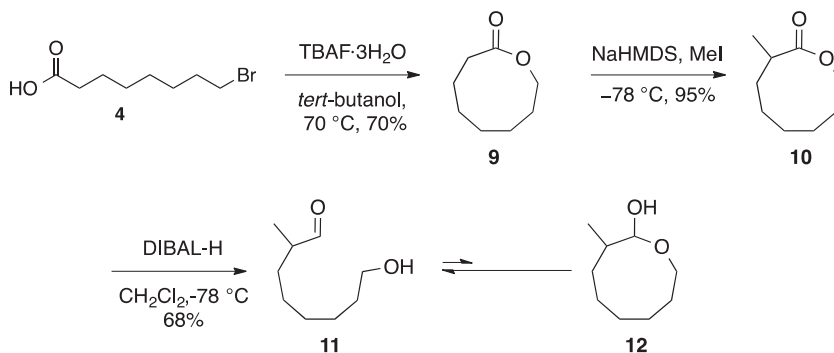
and **2**) predominantly gave the lactol tautomer. In contrast, large ring lactones favored the hydroxyaldehyde tautomer upon DIBAL reduction. These results are in complete agreement with literature observations.¹⁸ In all cases, a two-to-one equivalent ratio of the lactol **II** or hydroxyaldehyde **III** to the 2-hydroxy-1,4-hydroxynaphthoquinone (**2**) was crucial for complete alkylation (Scheme 4). Regardless of the tautomeric equilibrium composition of the DIBAL reduction products, the reactions were all high yielding. Also, whereas the reaction proceeded slowly at room temperature, refluxing in CH_2Cl_2 not only dramatically improved the yield, but also prevented the tetrahydropyranylation or tetrahydrofuranation of the terminal hydroxyl group (vide infra entry 1).

We also note that the yield from the alkylation reaction with butyrolactol was lower for the room temperature reaction and this was attributed to tetrahydrofuranation of the terminal hydroxyl group (Table 1, entry 1). The same result was observed, to a smaller extent, with valerolactol. The masking of the terminal hydroxyl group leading to the formation of **20** was not surprising considering the fact that the TCRA reaction employed 2 equiv of the lactol/hydroxyaldehyde in an acidic reaction medium. Thus, after the initial reductive alkylation reaction, the terminal hydroxyl reacts with either excess lactol or its hydroxyaldehyde tautomer to form **20**. However, at elevated



Scheme 3. Synthesis of lawsone derivative **13**.

temperatures the rate of hydrolysis (reverse reaction) is probably faster than that of tetrahydrofuranation. We attempted to slow down tetrahydrofuranation by reducing the aldehyde equivalents; however, in all cases a one-to-one ratio of aldehyde to hydroxynaphthoquinone **2** did not afford complete reaction even with extended reaction times. In any case, the overall yields of **19** and **21** could be improved by acid hydrolysis of their corresponding THP or THF ethers. Furthermore, because the products from TCRA reactions contain both enolic and terminal hydroxyl groups,



Scheme 2. Synthesis and DIBAL reduction of lactone **10**.

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