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Synthesis and antiplasmodial evaluation of cyclopropyl analogs of the G-factor bicyclic peroxide

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ABSTRACT

New bicyclic peroxyketal comprising cyclopropyl moieties, analogs of the G3-factor, have been synthesized and evaluated against *Plasmodium falciparum*. They exhibit modest antimalarial activities. In order to investigate their mode of action, Fe(II) induced reduction was managed allowing us to establish mechanisms involved on the basis of the structure of the final products. Self-quenching and polymerization seem to be the major degradation ways.

1. Introduction

Malaria is still a major health problem in tropical and subtropical regions, even though the number of deaths has decreased from about one million in 2000 to 655,000 in 2011.[1] As malaria parasites are developing resistances to several drugs even including the commonly used artemisinin,[1] new antiparasitic molecules are urgently required. As part of our work, taking aim at designing new antimalarial compounds acting as artemisinin, we have been interested in new analogs of the natural phytohormone extracted from *Eucalyptus grandis* known as G3-factor.[2] Previous studies have shown that the methylation[3] and the benzylation[4] of the peroxyhemiketal function were crucial for the antimalarial activity (IC_{50} of G3: 30 μM and IC_{50} of G3Me: 0.28 μM on Nigerian strain, IC_{50} of G3Bn: 0.21 μM on Nigerian strain and 0.37 on 3D7 strain). α-Spiro endoperoxides were also synthesized but without improvement of the G3Me activity.[5] Both electrochemical and chemical reductions of these compounds have been studied. Cyclic voltammetry studies on G3 and G3Me have shown, in both cases, a competition between concerted and stepwise mechanism during the electron transfer.[6] Theoretical study showed that the electron is first transferred into of the π* conjugated double bond and then in the O–O bond leading to its homolytic cleavage.[7] Iron(II)-induced reduction using conditions mimicking biological ones (1 equiv $FeSO_4$ in acetonitrile/water: 1/1), revealed that after homolytic cleavage of the O–O bond, an *O*-centered radical is formed, which quickly evolves to a centered radical, as described in Scheme 1.[8] Pathway (a) is exclusively present for G3 reduction whereas pathway (a) and (b) are present for G3Me and G3Bn reduction. We have shown that the alkylating properties of the *C*-centered radical rely on a good balance between stability and reactivity and could be correlated to the antimalarial activities of the G-factor analogs studied.

In the course of this program, we describe herein the synthesis and biological evaluation of cyclopropyl endoperoxide analogs with the aim of obtaining after iron(II) reduction, primary *C*-centered radical, which could be good alkylating agent for heme or vital proteins in the parasite (Scheme 2).

1.1. Preparation of the cyclic ketones

The methodology to synthesize these compounds was adapted from the one previously described for the G3-factor,[9] based on an autoxidation step by triplet dioxygen on dienol precursor.

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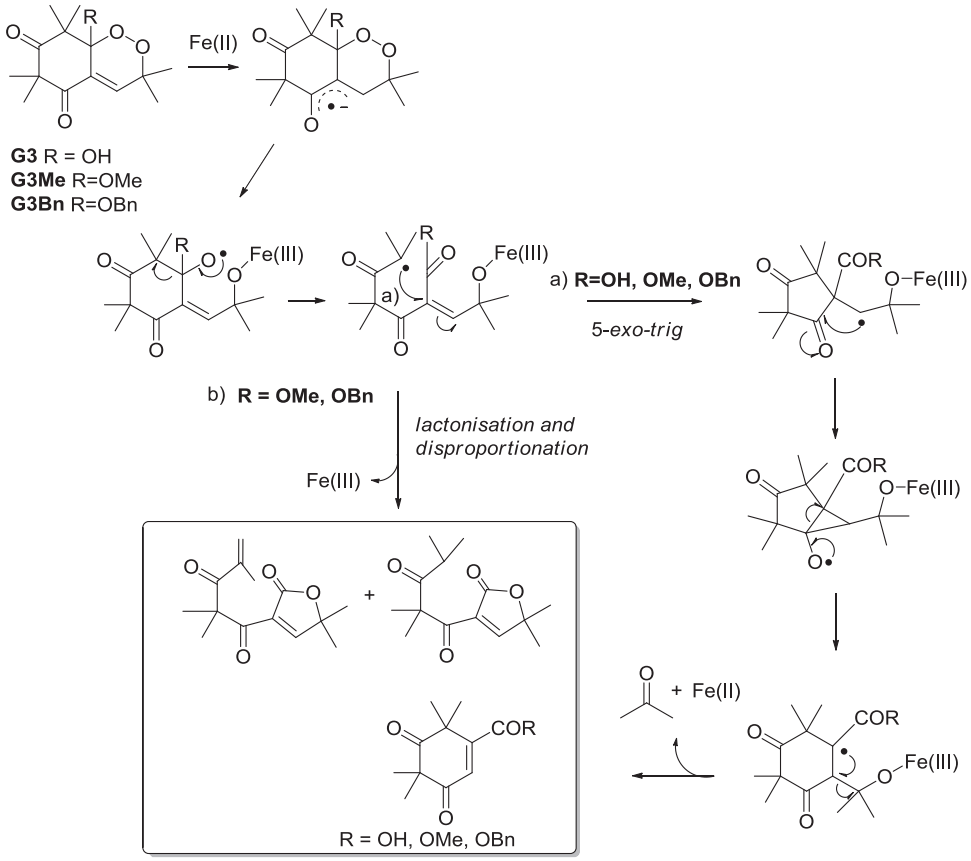
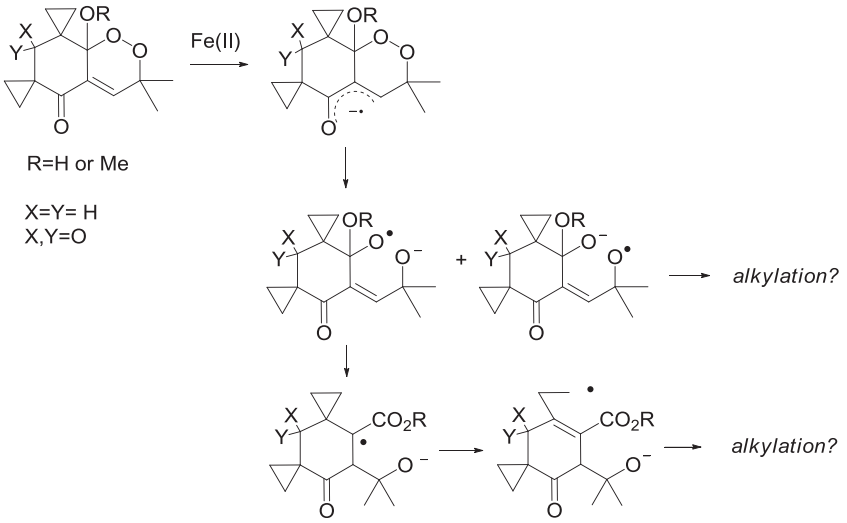


Scheme 1. Fe(II) induced reduction of G3, G3Me, and G3Bn.

The dienol can be prepared by a Mannich-type reaction between the triketone, isobutyraldehyde and piperidine. Preparation of cyclohexanedione and cyclohexanetrione was achieved following Beaudegnies synthesis[10] (Scheme 3).

*1.1.1. Preparation of 2,4-di-(spirocyclopropane)-cyclohexane-1,5-dione (**4**).* 2,4-Di-(spirocyclopropane)-cyclohexane-1,5-dione (**4**) started by a homologation of the bromo-ethyl-methacrylate into iodo-analog, **1**, following Knochel procedure[11] revised by Beaudegnies. The optimization of this step has been necessary in order to avoid the formation of dimer **1a**[12] and the recovery of the starting material. In fact the conditions proposed by Beaudegnies (Zn/CH_2I_2:1/1eq) gave the expected product but with unreacted starting material and we were not able to separate the two molecules. Finally, compound **1** was obtained in 98% yield, by using, Zn/CH_2I_2:4/4 equiv at 25 °C and slowly adding the Zn suspension into the acrylate at −20 °C.

Compound **2** was easily obtained in 75% yield by condensation of the anion of the 2-acetyl-γ-butyrolactone via a Michael addition on the electron deficient olefin followed by cyclopropanation and



Scheme 2. Hypothesis of primary *C*-centered radical formation after Fe(II) induced reduction.