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Bicyclic peroxides in the G factors series: synthesis and electrochemical studies

Monica Gavrilan,[a] Christiane André-Barrès,[a,*] Michel Baltas,[a,*] Théodore Tzedakis[b] and Liliane Gorrichon[a]

[a]*Laboratoire de Synthèse et de Physicochimie de Molécules d'Intérêt Biologique, CNRS et Université Paul-Sabatier, 118 route de Narbonne, 31062 Toulouse, France*

[b]*Laboratoire du Génie Chimique, CNRS et Université Paul-Sabatier, 118 route de Narbonne, 31062 Toulouse, France*

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Abstract—Endoperoxides belonging to the family of G factors have been synthesised under Mannich type conditions. The structure of different diastereoisomers has been established on the basis of NMR experiments. Their cathodic peak potentials have been determined by thin-layer electrochemistry under potentiostatic conditions, and compared to that of artemisinin. © 2001 Published by Elsevier Science Ltd.

Chemical investigations[1,2] on natural products extracted from Eucalyptus species have shown that, in addition to terpenes, flavonoids, polyphenolic compounds and secondary metabolites, new endoperoxides can be isolated (Fig. 1). These compounds, first extracted from *Eucalyptus grandis* and called **G** factors, act as phytohormones and growth regulators. They are considered to be involved in plant defense[3–5] (frost resistance) and they participate in plant regulation by an auxin-like activity[6] or an inhibitory effect that was found to be dependent on their concentration level.

It has been shown[7] that these peroxides, despite their toxicity for the plant, are synthesised in situ. They are probably present in an inactive form and readily released if necessary. The biochemical pathways allowing an intermediate to be oxidised or to the peroxides to be metabolised are still unknown.

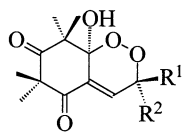
Two diastereomers G1 and G2 were isolated, but their stereochemistry was not found to be essential to their activity.[7]

A spontaneous oxidation by atmospheric dioxygen was also observed when a chemical synthesis of the ethylenic cyclohexanetrione precursors was performed allowing a facile access to G1, G2 and G3. Some natural substrates are known to react spontaneously with O_2.[8]

In connection with our work on this topic[9–11] and taking into account the biological interest of such compounds and the intriguing question of dioxygen addition, we report the synthesis of G analogues **7a**, **7b**, **8a** and **8b**. For compound **7**, a methyl group has been changed to a phenyl in order to extend the conjugation in the dienic intermediate **5**; for **8** the methyl was replaced by a very encumbered group, CH_2OSi*t*-$Bu(Ph)_2$.

We wish to check whether these modifications can influence the peroxide synthesis and the redox properties; our preliminary studies presented here are related to the electrochemical properties of the peroxides, mainly their reduction potential.

The synthesis of the target compounds was undertaken in two different ways. The first one (method (a)) is based on a Knoevenagel reaction between syncarpic acid **1** and the three aldehydes, isobutyraldehyde (**2**),



R^1	R^2	
Me	Et	G1
Et	Me	G2
Me	Me	G3

Figure 1. Structures of G-regulators, G1, G2 and G3 extracted from *Eucalyptus grandis*.

Keywords: peroxides; electrochemistry; G factors; oxygen uptake.

* Corresponding authors. Fax: 05 61 55 82 45; e-mail: candre@ramses.ups-tlse.fr; baltas@iris.ups-tlse.fr

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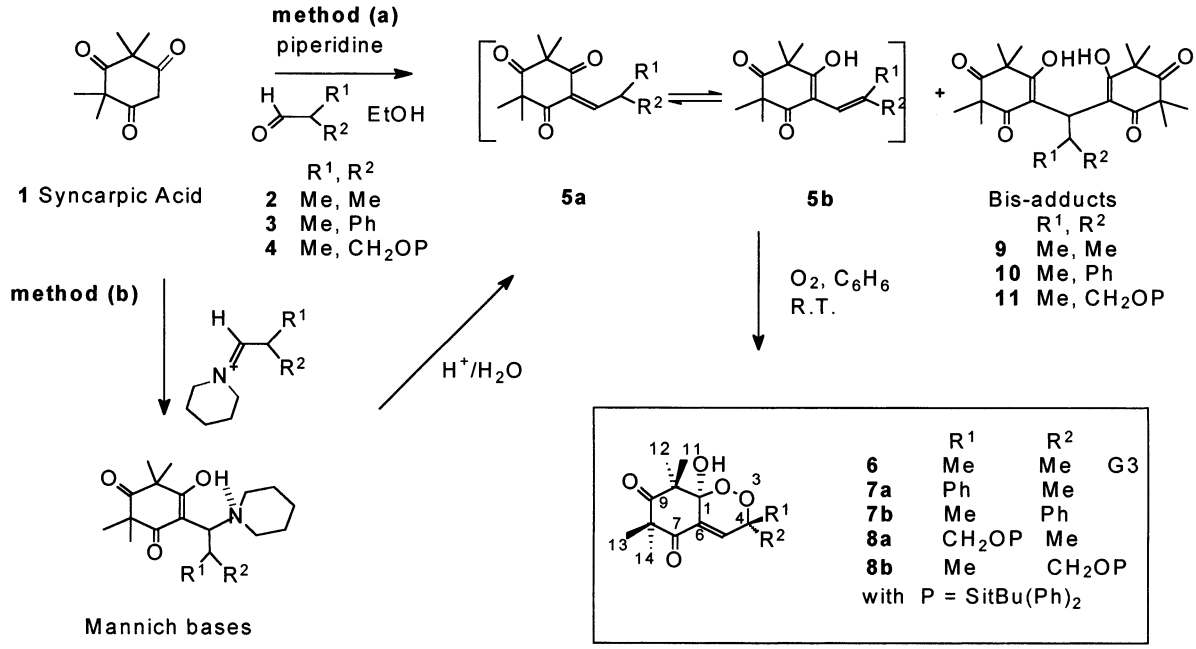

Scheme 1. Synthesis of endoperoxides **6**, **7**, **8** by method (a) and (b).

(±)-2-phenylpropionaldehyde (**3**) and (±)-2-methyl-3-[(*tert*-butyldiphenylsilyl)-oxy]propanal (**4**), in the presence of a catalytic amount of piperidine (Scheme 1), followed by spontaneous oxygen uptake leading to the expected endoperoxides **6**, **7** and **8**. An improved synthesis of syncarpic acid and of the G1, G2 and G3 cyclic peroxides by that method had been proposed earlier.[9] According to this methodology (method a), the Knoevenagel reactions have to be stopped at the monoaddition stage. Michael additions on the ethylenic ketones resulting from the condensation were minimised by the addition of a large excess of aldehydes (5–20 equiv.). However, the purification of compounds **5** in the presence of the higher boiling point aldehydes **3** and **4** became tedious. Several procedures have already been described to circumvent the problem, the enone being masked in a reversible way. Fuchs and Paquette[12] reported a general procedure for trapping the intermediates by using thiophenol; the reaction is followed by an oxidation step to regenerate the enone. The authors observed no bis-adduct. Secondary amines have also been used for this purpose by Bolte et al.[13] who have utilised the Mannich reaction in aprotic media. We preferred this last methodology (method (b)), which affords an easy release of the ethylenic ketones under acidic conditions from the Mannich bases (Scheme 1).

The bis-adduct was never observed; the yields are higher than with the previous method and the purification is easier (Table 1). For endoperoxides **6** and **7**, the starting aldehydes are commercially available while, for endoperoxide **8**, the (±)-2-methyl-3-[(*tert*-butyldiphenylsilyl)-oxy]propanal **4** was synthesised in two steps starting from (±)-2-methyl-1,3-propanediol; one of the hydroxyls was protected and the second oxidised to give **4** in 75% overall yield. Reaction of (±)-**3** and (±)-**4** with syncarpic acid (method (b)) leads, after removal of piperidine in protic acid medium to precursors **5**. The addition of the molecular dioxygen occurs more or less rapidly, depending on the dienols **5**, and yields the corresponding endoperoxides in one day for compound **6**, four days for compounds **7** and eight days for compounds **8**. After oxygen uptake, two diastereomeric peroxides **7a**, **7b** and **8a**, **8b** are obtained in overall yields of 70 and 60%, respectively, and in ratios of 60:40 and 75:25; the isomers were separated by chromatography.

The structure determination for each isomer was based on NMR observations.[14]

In each example, the endoperoxides are formed without addition of any sensitiser, with or without solvent, and in the dark. We found that UV irradiation, always without sensitiser, facilitates oxygenation of the enol. Compounds **8a** and **8b** were obtained in four hours after UV irradiation (300 nm), while it takes eight days without irradiation to obtain the same transformation ratio (10% of starting material recovered in both cases).

When a catalytic (2% in weight) or stoichiometric amount of DABCO was introduced under standard conditions, a very efficient singlet oxygen quencher, the endoperoxide synthesis was not inhibited. An important point must also be noted: no peroxide appeared when

Table 1.

$[\%]_{endoperoxide}$:$[\%]_{bis\ adducts}$	**6**:**9**	**7**[a]:**10**	**8**[a]:**11**
Method (a)	70:–	44[b]:46	10[b]:60
Method (b)	85:–	70:–	60:–

[a] **7a**:**7b**, 60:40; **8a**:**8b**, 75:25.
[b] 5 equiv. of aldehyde were added.

the dienol **5b**, in equilibrium with the enone **5a**, was methylated. To check if this oxidation is base catalysed, HCl was added in the reaction mixture, but the reaction was not quenched.

Thus, a major singlet oxygen contribution to the oxygen addition mechanism appeared to be rather unlikely. This point is also in agreement with other observations, by Snider,[15] related to the oxygenation of a dienol involved in the synthesis of chondrillin or plakorin. The hypothesis that the reaction occurs by a spin-allowed triplet–triplet Diels–Alder reaction between an excited state of the dienol and oxygen is discarded in our case, as the reaction occurs in the dark. It is likely that **5** behaves as a *radicaloid*, i.e. would be characterised by low lying excited states which interfere with the ground state.

Taking into account that electron transfer can play a significant role in cyclic endoperoxide activity, accurate values of their reduction potential are of interest. Even if thermochemical cycles are needed to estimate their standard reduction potential, determining the cathodic peak potential (E_p) can provide a first preliminary approach. In our case, five bicyclic endoperoxides, **6**, **7a**, **7b**, **8a** and **8b** have been studied and compared to artemisinin, using the electrochemical thin-layer method under potentiostatic conditions. Artemisinin[16–19] was chosen as a reference since it was recently studied by electrochemical methods in connection with its antimalarial activity.

Thin-layer electrochemistry[20–22] has several advantages. Due to the low volume of solution needed in the experiment, it is possible to transform all the electroactive molecules present in solution, in a relatively short time and, particularly, when the scanning rate is well suited to the selected concentration range while the current–potential curve is being plotted. We can also measure the number of electrons exchanged in the cathodic step.

The working electrode was a carbon film set between two glass slides delimiting a compartment with a volume of a few tens of μL. The choice of carbon was justified by the high cathodic overvoltages in DMF (−2 V with respect to a saturated calomel electrode SCE).

In a typical experiment, the electrochemical cell was placed under an inert atmosphere (N_2 at 1.5 atm) and the reduction was performed in the absence of oxygen in DMF containing 0.3 M tetraethylammonium perchlorate.

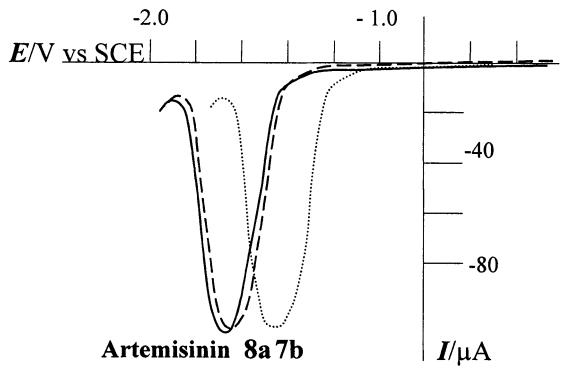

Figure 2. Current–potential curves obtained under 1.5 atm of N_2, with a thin film of carbon enclosed in a thin-layer cell. 0.3 mol L^{-1} of $NEt_4^+ClO_4^-$ in DMF; [endoperoxide] 0.01 mol L^{-1}; $T \sim 20°C$; $r = 0.5$ mV s^{-1}; $47 \leq V_{\text{thin layer}}$ (μL) ≤ 50.

The curves (Fig. 2), obtained with endoperoxide solutions, show peaks with potential values (E_p) in the range −1.45 to −1.68 V versus SCE (Table 2). The integration of each cathodic peak, corresponding to the charge delivered during the reduction step, leads to one electron per molecule of endoperoxide, in accordance with an initial formation of a radical anion of very short lifetime and a dissociative electron transfer mechanism[24] of the type $AB+e^- \rightarrow A^{\bullet}+B^-$.

The potential peak values for artemisinin determined by thin-layer electrochemistry or by cyclic voltammetry are identical (−1.68 V versus SCE) and one electron was also exchanged. All the values for the endoperoxides tested in the G series are the same or higher to the artemisinin one. Cleavage of the O–O bond for **6**, **7a** and **7b** occurs more than 0.20–0.25 V higher than for artemisinin, so that the dissociative reduction processes could be greatly facilitated. Additional electrochemical experiments on the estimation of standard reduction potential, determination of cathodic coefficient α and activation parameters and use of electron transfer mediators are under investigation. Finally, products formed during electrolysis will be characterised.

In conclusion, new endoperoxides belonging to the family of G factors have been characterised and the Mannich reaction is an efficient way to obtain the enone–dienols acting as intermediates. Although it can still be discussed, our first observations agree with the hypothesis of a triplet oxygen involved in the addition of O_2 to the dienol and the oxygen uptake still occurs when a methyl group on the lateral arm of the dienol was changed. Thin-layer electrochemistry appeared to

Table 2.

	6	**7a**	**7b**	**8a**	**8b**	Artemisinin
E_p (V) versus SCE (±10 mV)	−1.50	−1.49	−1.45	−1.62	−1.61	−1.68[a]

[a] The same value was obtained by cyclic voltammetry, by Workentin.[23]

be a convenient method to test the redox properties of these new compounds.

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14. HSQC and HMBC ^{1}H–^{13}C COSY experiments allow partial assignment of ^{1}H and ^{13}C spectra, whereas differentiation between methyls in each *gem*-dimethyl groups was based on NOESY spectra, as well as determination of the stereochemistry of each diastereomer **7a**, **7b**. Furthermore, a shielding effect ($\Delta\delta = 0.39$ ppm) on one of the methyl groups and a deshielding effect on the ethylenic proton were observed for the major compound **7a** and they have been attributed to the anisotropy of the phenyl group; these results agree with a configuration in which OH and Ph are in a *trans* relationship, (with respect to the endoperoxidic cycle) and the Me (in position 11) is oriented in the anisotropy cone of the phenyl group. For compound **7b** no such effect appeared and a *cis* relationship between the OH and Ph groups is proposed. **7a** ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.67$ (s, 1H, C=C*H*), 7.34 (m, 5H, Ar), 3.80 (s, O*H*), 1.64 (s, 3H, CH_3 in position 15), 1.41 (s, 3H, CH_3 in position 14), 1.37 (s, 3H, CH_3 in position 13), 1.24 (s, 3H, CH_3 in position 12), 0.74 (s, 3H, CH_3 in position 11). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta =$ 210.7 (C9), 198.6 (C7), 141.6 (C5), 141.4, 128.6, 128.1, 125.6 (Ar); 132.4 (C6), 97.5 (C1), 82.3 (C4), 55.0 (C8), 51.9 (C10), 26.7 (C14), 26.2 (C15), 24.3 (C13), 20.6 (C11), 15.0 (C12). **7b** ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.46$ (s, 1H, C=C*H*), 7.40 (m, 5H, Ar), 3.70 (s, O*H*), 1.87 (s, 3H, CH_3 in position 15), 1.39 (s, 6H, CH_3 in position 13–14), 1.36 (s, 3H, CH_3 in position 12), 1.13 (s, 3H, CH_3 in position 11). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 210.6$ (C9), 198.1 (C7), 141.9 (C5), 137.7, 129.4, 129.0, 126.4 (Ar), 131.5 (C6), 97.6 (C1), 82.6 (C4), 55.1 (C8), 51.9 (C10), 26.6, 24.0 (C13, C14), 23.3 (C15), 21.0 (C11), 15.1 (C12).
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