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Synthesis of antimalarial G-factors endoperoxides: relevant evidence of the formation of a biradical during the autoxidation step

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ABSTRACT

In the search for new antimalarial endoperoxides related to G-factors series, using a methodology based on autoxidation of a dienol sytem, unexpected cyclic ether alcohols and hydroperoxides were obtained confirming the structure of the previously postulated biradical intermediate implicated in oxygen uptake. Antimalarial activities of PMB-endoperoxides are greatly enhanced when the peroxyhemiketal function is methylated for the G3 endoperoxide.

1. Introduction

New antimalarial agents are still the subject of intensive research.[1] Since the isolation and discovery of the activity of artemisinin, the search for a new generation of artemisinin based therapeutics is being pursued by several research groups.[2] Recently synthetic peroxides including 1,2,4-trioxanes,[3] 1,2,4-trioxolanes,[4] tetraoxanes,[5] cyclic peroxyketals[6] and endoperoxides[7,8] were discovered. The antimalarial activity of all these compounds arises from ferrous iron-mediated bioactivation within the parasite food vacuole. Currently we have worked on modified endoperoxides belonging to the G-factors series in order to understand and possibly to improve their antiplasmodial activities. G-factors are natural endoperoxides first extracted from leaves of *Eucalyptus grandis*.[9] They are considered as phytohormones and growth regulators probably controlling the electron transport properties of membranes.[10] Some of the previously synthesized derivatives present moderate to good antimalarial activity. Several parameters were found to be important for their antimalarial potency: lipophilicity, redox potential involving one electron exchanged during O–O reduction,[11,12] and alkylation of the peroxyhemiketalic function.[13] In this latter case benzyl ether analogues (G3Bn) exhibited the highest activities (IC_{50}=300–100 nM on chloroquine sensitive and resistant strains, respectively) in the same value of magnitude between the two enantiomers and threefold better than the methylated ether (G3Me).[14] Concerning Fe(II)-reduction of the O–O bond, our mechanistic studies revealed two different pathways for the initially formed *C*-centred radical depending on the alkylation or not of the peroxyhemiketal function and on the substitution pattern of the peroxycycle.[15] Our studies have shown that the alkylating properties of the *C*-centred radical rely on a good balance between stability and reactivity and could be correlated to the antimalarial activities of the G-factors analogues studied.

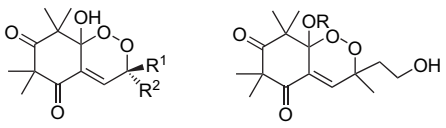
Moreover, aminoendoperoxides were found to be inactive thus questioning previous biological hypothesis suggesting that these functions could generally improve bioavailability by an accumulative effect in the parasite food vacuole.[16]

Our ongoing research program presents dual objectives (i) a mechanistic insight on the comprehension of the G-factors analogues formation, (ii) biological activity in relation to their structure. In that respect, we wish to report our efforts on exploration of the endoperoxide formation leading to new rearrangements and on the evaluation of the antimalarial activities.

This work relates our efforts on the functionalization of the lateral chain from the primary alcohol in the aim of attaching a second active molecule (Fig. 1).

2. Results and dicussion

Commercially available α-methyl-γ-butyrolactone may be considered as the starting compound for preparing the aldehydic



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

Figure 1. G-factors and functionalized endoperoxides.

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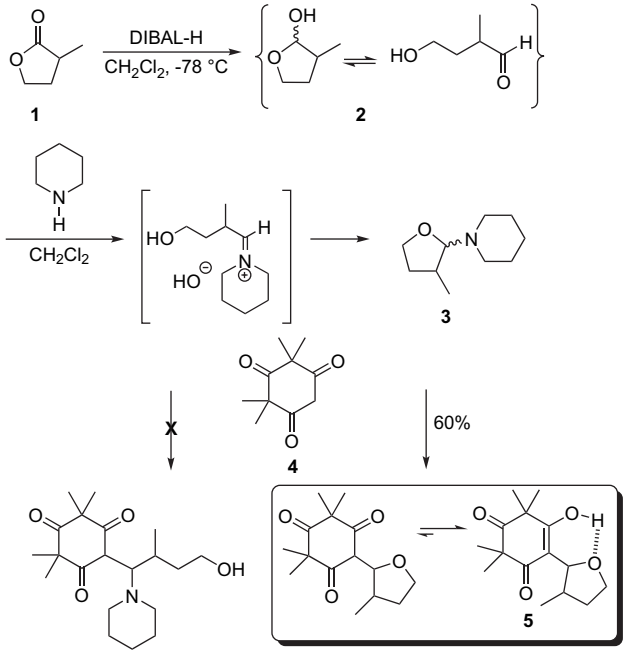
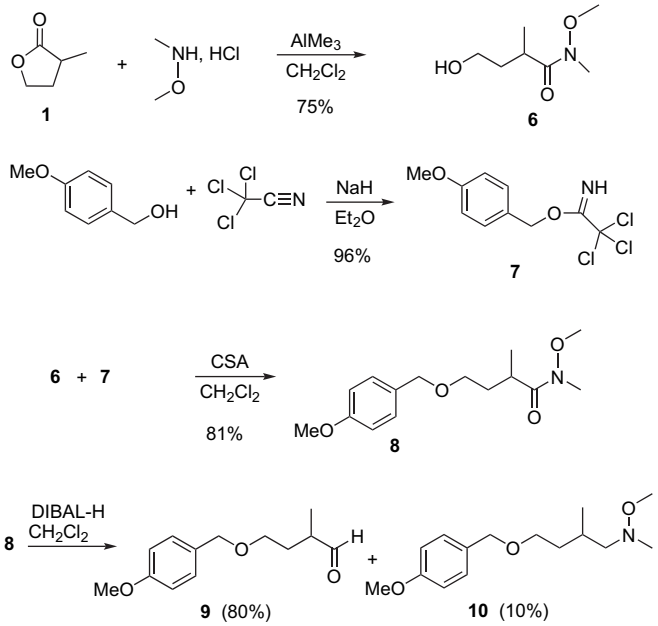
partner of syncarpic acid in the Knoevenagel-type reaction. Our efforts to operate without protecting groups proved to be unsuccessful (Scheme 1). In fact the thermodynamically favoured five-membered ring was in each case formed. Reduction of the lactone **1** in presence of DIBAL-H afforded lactol **2** in good yield. Lactol **2** was subjected to react under our reported sequence, piperidine and then syncarpic acid. No Mannich base was observed but bicyclic compound **5** was obtained in good yield as a diastereoisomeric mixture issued from hemiaminal **3**.

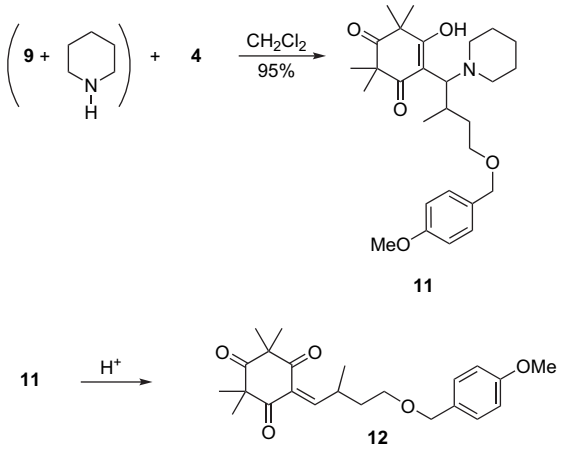


Scheme 1. Formation of bicycle **5** without use of protective group on primary hydroxyl.

We then decided to open the lactone via the formation of the Weinreb amide[17] (Scheme 2). Treatment of α-methyl-γ-butyrolactone with the aluminium salt of methoxymethylamine afforded the Weinreb amide **6** in good yield (75%). The protective group has to be introduced in neutral or acidic conditions in order to avoid



Scheme 2. Synthesis of aldehyde **9** via Weinreb amide.

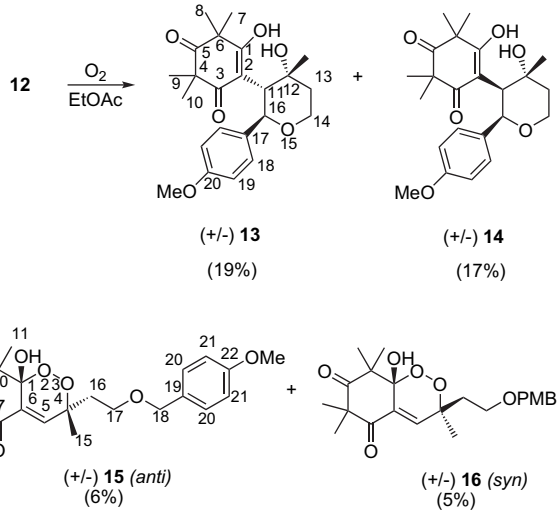


Scheme 3. Mannich base and ene-one synthesis.

cyclization into lactone **1**. It must be compatible with the following steps: acidic conditions, basic and reductive ones. It has to be cleaved selectively with respect to the peroxide bond, which excludes catalytic hydrogenation. The *para*-methoxybenzyl group (PMB) was chosen as it fulfils the required conditions. It was introduced via a mild protection method for hydroxyl functions using the *para*-methoxybenzyl trichloroacetimidate reagent (**7**), which was easily prepared from *para*-methoxybenzyl alcohol and trichloroacetonitrile in the presence of sodium hydride (10 mol %).[18] Weinreb amide **6** is then treated with the trichloroacetimidate derivative **7**, in the presence of camphorsulfonic acid (0.2 equiv)[19] and after 20 h the expected PMB protected product **8** was obtained in good yield (81%). The DIBAL-H reduction of the amide **8**, by the method reported by Hollenberg[20] provides the aldehyde **9** in good yield (80%) as well as compound **10** (10%) issued from the reductive amination of the desired aldehyde **9** with methoxymethylamine.

The modified Knoevenagel reaction between syncarpic acid and the iminium intermediate formed by aldehyde **9** and piperidine in equimolar quantities afforded the expected Mannich base in quantitative yield (Scheme 3). In aqueous acid, elimination of piperidine occurred affording the corresponding ene-one **12**. ^{1}H NMR spectrum showed no tendency to enolization. This methodology avoids production of bisadducts.[21]

Ene-one **12** was then subjected to different oxygen uptake conditions. First, as in previous experiments the solution of ene-one **12** was left under air at room temperature. The reaction was



Scheme 4. Procedure 1 for oxygen uptake.

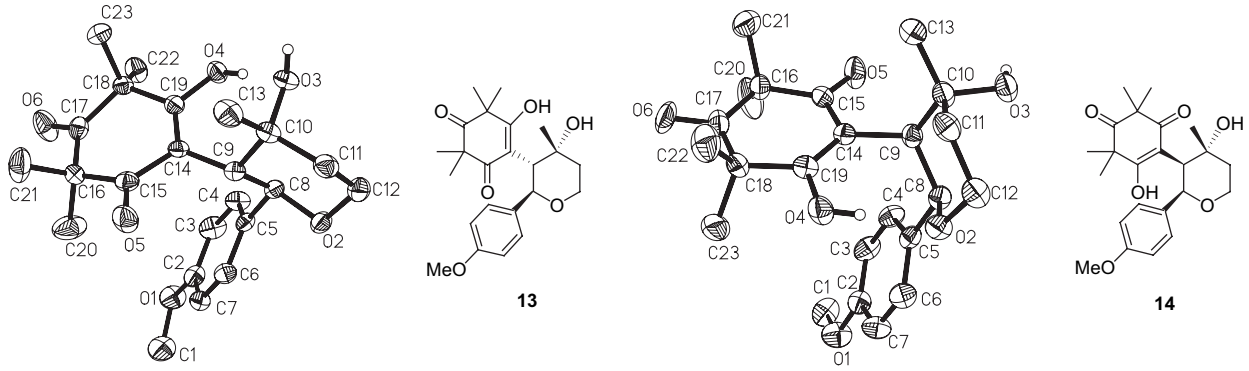


Figure 2. Molecular view of alcohols **13** and **14** in the solid state (thermal ellipsoids at 50% probability; hydrogen atoms are omitted for clarity).

followed by ^{1}H NMR until disappearance of the vinyl proton signal of ene-one **12**. After 13 days the reaction was complete. Surprisingly analyses of formed compounds show that oxygen uptake didn't proceed as usual. After column chromatography on silica gel, the major compounds isolated were diastereoisomeric cyclic ethers containing a tertiary hydroxyl group: **13** and **14** (19% and 17%, respectively) as well as just 11% of endoperoxides (Scheme 4).

Structures of these unexpected compounds were confirmed by X-ray diffraction of crystals[22] and relative configurations could be established (Fig. 2).

In an attempt to understand this peculiar rearrangement it was necessary to consider a precedent report concerning an EPR/spin trapping study of the spontaneous addition of dioxygen on the precursor of G3-factor.[26] During this study the use of nitroso and nitrone spin traps allowed the detection of two radical centres, providing the evidence that addition of dioxygen follows a radical pathway. Structures of biradical intermediates have been postulated and are presented in Figure 3.

Pursuing this hypothesis, a mechanism can be proposed in which biradical species participate but in this special case can evolve differently from the sole formation of endoperoxides as described in previous reports. The proposal of the mechanism of formation of these cyclic ethers **13** and **14** is based on the postulated biradical species of type **I** as intermediates (Scheme 5): oxidation of PMB and *inter* or *intra*-molecular reduction of the peroxide could lead to **13** and **14**. This autoxidation is quite slow (13 days) and the determining step is probably enolization.

Photoenolization in dichloromethane under argon is then carried out on ene-one **12** using Rayonet apparatus equipped with 350 nm low-pressure mercury lamps (Scheme 6).

Enolization was followed by ^{1}H NMR. After irradiation for 2 h, 90% of the enol form **12′** was obtained. Afterwards the solution was kept under air and aliquot was analyzed by ^{1}H NMR. Autoxidation was then quite fast since precursor **12′** disappeared after 24 h. Besides endoperoxides and cyclic ethers, a new compound was formed, which proved to be hydroperoxide **17** (Scheme 7). Only one

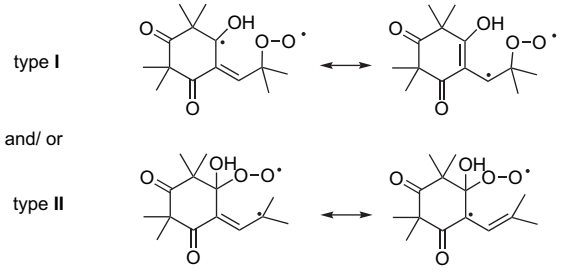
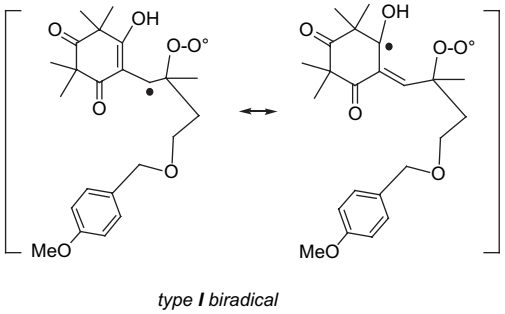
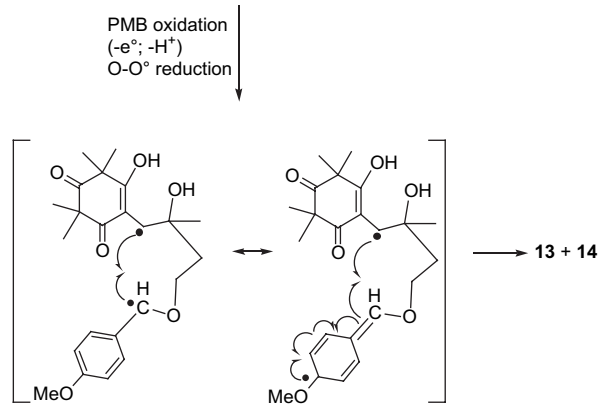


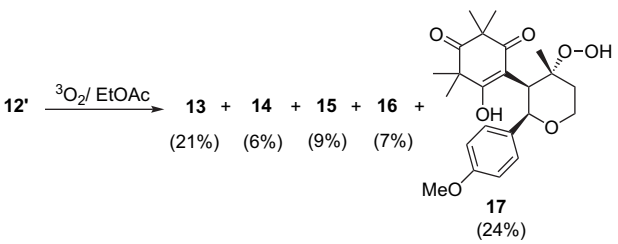
Figure 3. Proposal for structure of biradical species during autoxidation step.[26]





Scheme 5. Mechanism proposal for cyclic ethers **13** and **14** formation.

Scheme 6. Photoenolization at 350 nm.



Scheme 7. Procedure 2 for oxygen uptake.

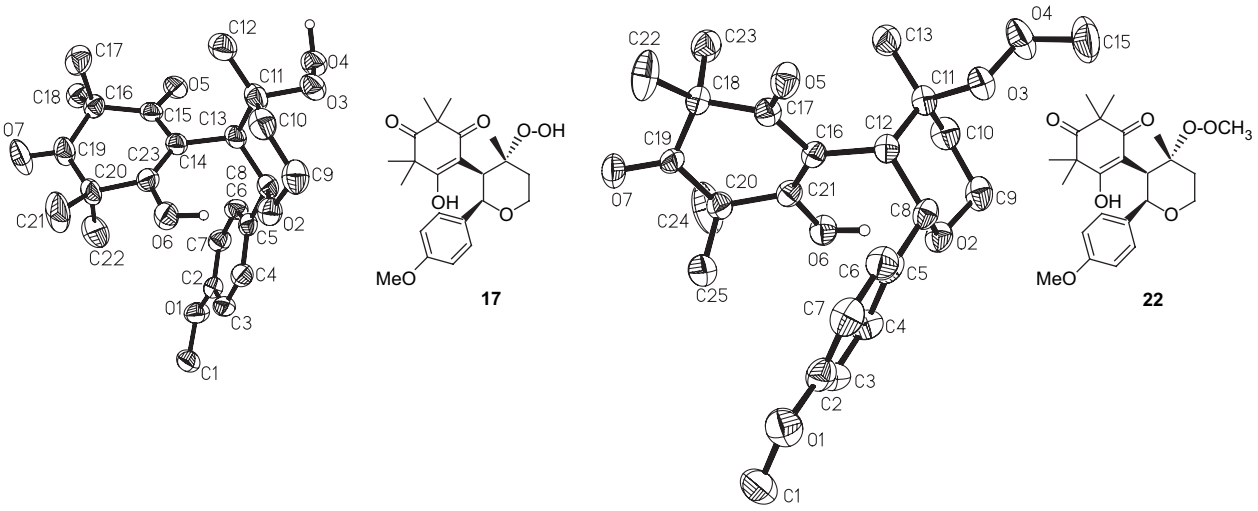


Figure 4. Molecular view of hydroperoxide **17** and peroxide **22** in the solid state (thermal ellipsoids at 50% probability; hydrogen atoms are omitted for clarity).

diastereoisomer could be isolated and its structure was confirmed by X-ray diffraction of crystals[22] (Fig. 4). This hydroperoxide was stable once isolated and purified but was reduced leading to **14** when left as a crude mixture after autoxidation. We suppose this is the reason why it was not isolated in procedure 1, as reaction time was quite long. Even if we haven't explained, we can notice that diastereoisomeric ratio for endoperoxides **15** and **16** was almost 1:1, which is significantly different from ratio obtained previously[16] with derivatives featuring O-Si^{t}Bu(Ph)$_2$ instead of O-PMB.

Finally photoenolisation in the presence of singlet oxygen following the Snider procedure for oxidation of dienol system[27] (Rose Bengal as sensitizer in dichloromethane/methanol) was attempted. The dienol precursor **12′** was quickly oxidized furnishing endoperoxides **15**/**16** as major compounds (34%) as well as cyclic ether alcohols **13**/**14** (27%) and hydroperoxide **17** (13%) (Table 1). Competition between reactivity of dienol **12′** towards triplet and singlet oxygen occurred. The reactivity of the postulated biradical intermediate formed during autoxidation cannot be completely bypassed and so cyclic ether alcohols and hydroperoxide were also formed. Others examples of oxygen uptake on similar systems can be found in the literature: for instance, Frimer[28] depicted photosensitized oxygenation of tetrasubstituted cyclopropenes included in large rings and Schobert[29] compared photooxygenation and radical autoxidation of 3-alkylidene dihydrofuran-2,4-diones leading to hydroperoxides and/or endoperoxides lactones.

Endoperoxides **15** and **16** obtained pure after silica gel chromatography were separately methylated on the peroxyketal position to furnish methylated endoperoxides **18** and **19**, respectively (Scheme 8). Endoperoxides **18** (*anti*: defined by OMe and CH_2CH_2OPMB on the opposite side of the heterocycle) and **19** (*syn*) were characterized and differentiated by HMBC (Heteronuclear Multiple Bond Correlation), HSQC (Homonuclear Single Quantum Correlation), and NOESY (Nuclear Overhauser Effect Spectroscopy) for the stereochemistry. NOE effect was observed between OMe and 15-Me for endoperoxide **18** while, for endoperoxide **19**, NOE effect was observed between OMe and CH_2. Likewise endoperoxides, hydroperoxide **17** was also methylated in the same basic conditions (BuLi/TfOMe) and methyl peroxide **22** was isolated in the aim to evaluate its antimalarial properties (Scheme 8). X-ray diffusion of crystals of **22** allowed us to determine its relative configuration (Fig. 4).[22]

Deprotection of the *para*-methoxybenzyl group was easily performed under oxidative conditions: dichlorodicyanobenzoquinone/water,[30] for each endoperoxide. Endoperoxides **20** and **21** were thus obtained in quantitative yield. Surprisingly, **21** was unstable under acidic conditions. Even on silica gel, this endoperoxide rearranged via 1,2-dioxetane in aldehyde and ketone. This sensitivity to acidic medium has also been observed previously in a *syn* series of silylated endoperoxides.[16]

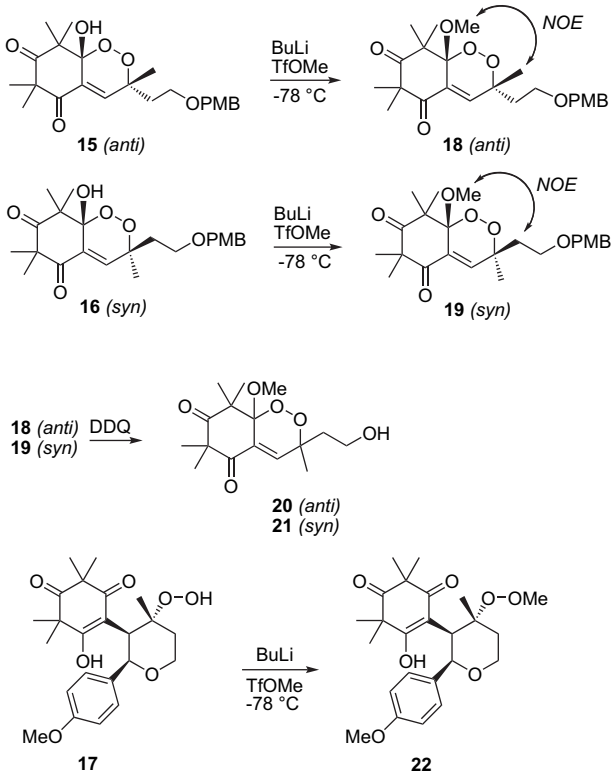
3. Antimalarial activity

Compounds **15**, **16**, **18**, **19** and **22** were tested in vitro against the Nigerian strain of *Plasmodium falciparum* (Table 2). The activity was determined by Desjardins et al.[31] using [^{3}H] hypoxanthine incorporation to assess parasite growth. Parasitic viability was expressed as IC_{50}, the drug concentration causing 50% parasite growth inhibition. Remarkably, antimalarial activity of the peroxyketal compounds **18** and **19** increased 20-fold when compared to the peroxyhemiketals **15**, **16**, which emphasize the crucial role of this methylation, and led us to believe that these compounds behave under Fe(II)-induced reduction in the same manner as G3 and G3Me.[14] When TBDPS instead of PMB was used as protective group, the biological activity was in the same range, around 1 μM, both for the hydroxylated and for the methylated endoperoxides,[16] which was significant of other radical mechanism pathways for the reduction of the O–O bridge. Only one deprotected diastereoisomer, **20**, could be tested as the other one, **21**, was unstable in acidic

Table 1
Yield of isolated products following the chosen procedure

Procedures	Conditions	Precursor **12** (%)	**13** (%)	**14** (%)	Alcohols **13**+**14** (%)	**15** (%)	**16** (%)	Endoperoxides **15**+**16** (%)	Hydroperoxide **17** (%)
1	Air 13 days; CH_2Cl_2	0	19	17	36			11[a]	0
2	Photoenolisation (350 nm) and then air (24 h); CH_2Cl_2	0	21	6	27	9	7	16	25
3	Photoenolisation (350 nm) and then $^1O_2$; CH_2Cl_2/MeOH	20	13	14	27	20	14	34	13

[a] Isolated together.



Scheme 8.

Table 2
IC_{50} values of several peroxides on Nigerian strains of *Plasmodium falciparum*

	15	**16**	**18**	**19**	**20**	**21**	**22**
IC_{50} (μM)	10.5	9.9	0.67	0.47	73[a]	nd[b]	3.7

[a] cf. Ref 16.
[b] Not determined (unstable in acidic medium).

medium. However, **20** lost antimalarial activity. Finally, methyl peroxide **22** possessing different structural frames showed a weak activity.

4. Conclusion

The autoxidation approach in order to synthesize functionalized endoperoxides related to the G-factors series did not lead to encouraging results in terms of synthetic methodology. Nevertheless from a fundamental point of view, the formation of new cyclic ether alcohols or hydroperoxides allowed us to pursue the comprehension of the reaction mechanism of this intriguing oxygen uptake. The previous proposal of a biradical intermediate[26] is reinforced. Moreover, antimalarial activity of methylated endoperoxides **18** and **19** are below the micromolar level and in the same range as methylated G3 (0.22 μM), which led us to think that the functionalized chain introduced does not bring steric hindrance either in the *syn* or in the *anti* series.

5. Experimental section

5.1. General

Melting points were measured on a Büchi and were uncorrected. The NMR spectra were recorded on a Brucker Avance 300 FT-NMR or Brucker Avance 400 or Brucker Avance 500 FT-NMR. LRMS data were obtained by DCI/NH_3 on a TSQ 7000 Thermoelectron, or by ESI on API 365 Perkin Elmer Sciex or Q-TRAP Applied Biosystems. HRMS were recorded by ESI on GC TOF Waters. IR spectra were recorded on a Perkin Elmer 1760-X. Products designation has been defined using ChemDraw Ultra 8.0 (Cambridge Soft/ Chem. Office 2004) software, which determines IUPAC nomenclature. Structures' numbering used for NMR spectra description doesn't follow IUPAC rules.

5.2. Tetrahydro-3-methylfuran-2-ol (2)

α-Methyl-γ-butyrolactone (2 g, 20 mmol) was solubilized in anhydrous dichloromethane (40 mL) under argon. DIBAL-H 1 M in dichloromethane (30 mL, 30 mmol) was added slowly at −78 °C and the solution was stirred at −78 °C for 4 h. Methanol (5 mL) and then silica gel/water (70 mL/5 mL) were added. Crude mixture was stirred for 2 h at room temperature, then filtered and evaporated in vacuo (P=40 mmHg, T=30 °C) to give lactol **2** as an uncoloured oil (1.53 g, 15 mmol) in 75% yield.

5.3. 4-(Tetrahydro-3-methylfuran-2-yl)-5-hydroxy-2,2,6,6-tetramethylcyclohex-4-ene-1,3-dione (5)

Lactol **2** (0.102 mg, 0.999 mmol) was solubilized in anhydrous dichloromethane (4 mL) at room temperature under argon. Piperidine (99 μL, 0.999 mmol) was added. Fifteen minutes later, syncarpic acid (0.182 mg, 0.999 mmol) and then H_2SO_4 (53 μL, 0.999 mmol) were added. The mixture was stirred for 48 h and then saturated $NaHCO_3$ solution was poured. After extraction with dichloromethane, the organic phase was washed with water, dried over $MgSO_4$, filtered and concentrated in vacuo. Compound **5** was obtained as a mixture of two diastereoisomers (0.157 mg, 0.589 mmol, 59%) and analyzed without any treatment.

5.3.1. Diastereoisomer 1

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.76 (d, 3H, CH_3CH, $^3J_{HH}$=7.2 Hz), 1.30 (s, 6H, 2CH_3), 1.42 (s, 6H, 2CH_3), 1.74 (m, part of ABX system, 1H, CH_2–CH_2O), 2.27 (m, part of ABX system, 1H, CH_2–CH_2O), 2.75 (m, 1H, CH_3CH), 3.92–4.08 (m, ABX system, 2H, CH_2O), 4.96 (d, 1H, CHO, $^3J_{HH}$=5.2 Hz); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 11.88 (CH_3CH), 24.50 (2CH_3), 25.41 (2CH_3), 32.89 (CH_2CH_2O), 35.62 (CHCH_3), 50.20 (C_q), 54.79 (C_q), 66.48 (CH_2O), 83.48 (CHO), 106.62 (C=COH), 176.36 (C=COH), 197.24 (C=O), 213.16 (C=O); MS (DCI/NH_3, DCM) m/z: 301 $[MN_2H_7]^+$, 284 $[MNH_4]^+$, 267 $[MH]^+$.

5.3.2. Diastereoisomer 2

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (d, 3H, CH_3CH, $^3J_{HH}$=6.6 Hz), 1.31 (s, 6H, 2CH_3), 1.41 (s, 6H, 2CH_3), 1.71 (m, part of ABX system, 1H, CH_2–CH_2O), 2.09 (m, 1H, CH_3CH), 2.19 (m, part of ABX system, 1H, CH_2–CH_2O), 3.92–4.08 (m, ABX system, 2H, CH_2O), 4.75 (d, 1H, CHO, $^3J_{HH}$=7.9 Hz); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 16.87 (CH_3CH), 24.09 (2CH_3), 24.87 (2CH_3), 34.06 (CH_2CH_2O), 41.29 (CHCH_3), 50.20 (C_q), 54.79 (C_q), 67.26 (CH_2O), 84.26 (CHO), 108.71 (C=COH), 175.60 (C=COH), 197.24 (C=O), 212.94 (C=O); MS (DCI/NH_3, DCM) m/z: 301 $[MN_2H_7]^+$, 284 $[MNH_4]^+$, 267 $[MH]^+$.

5.4. 4-Hydroxy-*N*-methoxy-*N*,2-dimethylbutanamide (6)

Trimethylaluminium (5 mL, 10 mmol) was added at 0 °C to *N*,*O*-dimethylhydroxylamine (976 mg, 10 mmol) in dichloromethane (35 mL). After 30 min at room temperature, α-methyl-γ-butyrolactone (100 mg, 4 mmol) in dichloromethane (10 mL) was added to the mixture. After 24 h silica gel was added and then filtered. Weinreb amide **6** (485 mg, 3.009 mmol) was obtained in 75% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (d, 3H, CH_3–CH, $^3J_{HH}$=7.0 Hz), 1.80 (m, ABX system, 2H, CH_2), 3.10 (m, 1H, CH–CH_3), 3.20 (s, 3H,

N–CH_3), 3.64 (m, 2H, CH_2OH), 3.72 (s, 3H, NO–CH_3); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 17.42 (*C*H_3–CH), 32.26 (NCH_3), 32.98 (*C*H–CH_3), 36.07 (CH_2), 60.55 (CH_2–OH), 61.57 (NO–CH_3), 178.48 (C=O); MS: (DCI/NH_3) *m*/*z*: 162 $[MH]^+$, 179 $[MNH_4]^+$.

5.5. *p*-Methoxybenzyl trichloroacetimidate (7)

Sodium hydride (60% in oil, 40.2 mg, 1.01 mmol) was added under argon to *p*-methoxybenzyl alcohol (556 mg, 4.024 mmol), which was previously solubilized in anhydrous ether (1.5 mL). The mixture was stirred for 30 min at room temperature and then cooled at 0 °C. Trichloroacetonitrile (403 μL, 4.024 mmol) was then added. When room temperature was reached, the mixture was stirred for 2 h, then neutralized with saturated $NaHCO_3$ solution and extracted with diethyl ether. Organic layer was dried over $MgSO_4$ and concentrated to obtain the trichloroacetimidate (1.090 g, 3.858 mmol, 96%) as oil. R_f (petroleum ether/AcOEt: 1:1) 0.78; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.71 (s, 3H, CH_3O), 5.18 (s, 2H, CH_2O), 6.81 (d, 2H, 2CH aromatics, $^3J_{HH}$=8.7 Hz), 7.27 (d, 2H, 2CH aromatic).

5.6. 4-(4-Methoxybenzyloxy)-*N*-methoxy-*N*,2-dimethylbutanamide (8)

p-Methoxybenzyl trichloroacetimidate (**7**) (987 μL, 4.754 mmol) and then camphorsulfonic acid (69 mg, 0.297 mmol) were added to Weinreb amide **6** (479 mg, 2.971 mmol) in dichloromethane (30 mL). After 20 h, the mixture was diluted with diethyl ether and then treated with $NaHCO_3$. After extraction with diethyl ether, organic phases were dried over $MgSO_4$, filtered and then concentrated. Crude product was purified on silica gel (petroleum ether/AcOEt: 7:3 then 1:1) to furnish the pure compound **8** (673 mg, 2.392 mmol, 81%) as yellow oil. R_f (petroleum ether/AcOEt: 7:3) 0.19; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (d, 3H, C*H*$_3$–CH, $^3J_{HH}$=6.9 Hz), 1.67 (m, ABX system, 1H, C*H*$_2$–CH_2O), 2.01 (m, ABX system, 1H, C*H*$_2$–CH_2O), 3.15 (m, 1H, C*H*–CH_3), 3.17 (s, 3H, N–CH_3), 3.45 (m, 2H, CH_2–C*H*$_2$O), 3.65 (s, 3H, NO–CH_3), 3.80 (s, 3H, PhOC*H*$_3$), 4.40 (s, 2H, OC*H*$_2$–Ph), 6.86 (d, 2H, CH aromatic, $^3J_{HH}$=8.7 Hz), 7.83 (d, 2H, CH aromatic, $^3J_{HH}$=8.7 Hz); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 17.64 (*C*H$_3$–CH), 32.05(NCH_3), 32.05 (*C*H–CH_3), 33.56 (CH_2–CH_2O), 55.29 (*C*H$_3$OPh), 61.45 (NO–*C*H$_3$), 67.95 (CH_2–*C*H$_2$O), 72.53 (Ph–*C*H$_2$O), 113.73 (2CH, aromatic), 129.27 (2CH, aromatic), 130.64 (C, aromatic), 159.13 (C, *C*OCH$_3$), 177.66 (C=O); IR (thin film) ν 2966–2868 (CH_2 and CH_3), 2839 (OCH_3), 1659 (C=O, amide), 1613, 1586 and 1513 (C=C aromatic), 1248 and 1117 (C–O) cm^{-1}; MS (DCI/NH_3) *m*/*z*: 282 $[MH]^+$, 299 $[MNH_4]^+$; HRMS (IS, MeOH): calculated for $C_{15}H_{24}NO_4$ 282.1705, found 282.1724; calculated for $C_{15}H_{23}NO_4Na$ 304.1525, found 304.1496.

5.7. Reduction of Weinreb amide (8)

DIBAL-H 1 M in toluene (6.9 mL, 6.824 mmol) was added at −78 °C to Weinreb amide **8** (480 mg, 1.706 mmol) in dichloromethane (35 mL). After 75 min, the mixture was treated with methanol, water and then HCl (1 N) then extracted with dichloromethane. The organic phase is washed with water, then dried over $MgSO_4$, filtered and concentrated. Column chromatography on silica gel (petroleum ether/AcOEt: 17:3) allowed to separate aldehyde **9** and *N*-methoxy-amine **10** (45 mg, 0.171 mmol, 10%). Aldehyde (303 mg, 1.365 mmol, 80%) was obtained as yellow oil.

5.7.1. 4-(4-Methoxybenzyloxy)-2-methylbutanal (***9***)

R_f (petroleum ether/AcOEt: 7:3) 0.55; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (d, 3H, C*H*$_3$–CH, $^3J_{HH}$=7.1 Hz), 1.69 (m, ABX system, 1H, C*H*$_2$–CH_2O), 2.02 (m, ABX system, 1H, C*H*$_2$–CH_2O), 2.54 (m, 1H, C*H*–CH_3), 3.50 (m, 2H, CH_2–C*H*$_2$O), 3.80 (s, 3H, PhOC*H*$_3$), 4.41 (s, 2H, OC*H*$_2$–Ph), 6.87 (d, 2H, CH aromatic, $^3J_{HH}$=8.7 Hz), 7.23 (d, 2H, CH aromatic, $^3J_{HH}$=8.7 Hz), 9.63 (d, 1H, CHO, $^3J_{HH}$=1.7 Hz); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 13.28 (*C*H$_3$–CH), 30.87 (CH_2–CH_2O), 43.80 (*C*H–CH_3), 55.30 (*C*H$_3$OPh), 67.09 (CH_2–*C*H$_2$O), 72.53 (Ph–*C*H$_2$O), 113.80 (2CH, aromatic), 129.22 (2CH, aromatic), 130.31 (C, aromatic), 159.22 (C, *C*OCH$_3$), 204.79 (C=O); IR (thin film) ν 2952–2835 (CH aliphatic), 2711 and 1725 (CH and HC=O), 1612, 1586 and 1513 (C=C aromatic), 1248 and 1173 (C–O) cm^{-1}; MS (DCI/NH_3) *m*/*z*: 240 $[MNH_4]^+$; HRMS (IS, MeOH): calculated for $C_{13}H_{18}O_3Na$ 245.1154, found 245.1140.

5.7.2. 4-(4-Methoxybenzyloxy)-N-methoxy-N,2-dimethylbutan-1-amine (***10***)

R_f (petroleum ether/AcOEt: 7:3) 0.60; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (d, 3H, C*H*$_3$–CH, $^3J_{HH}$=6.6 Hz), 1.41 and 1.81 (m, ABX system, 1H, CH_2, C*H*$_2$–CH_2O), 1.88 (m, 1H, C*H*–CH_3), 2.43 (m, 2H, C*H*$_2$NOCH$_3$), 2.54 (s, 3H, NC*H*$_3$), 3.50 (s, 3H, NOC*H*$_3$), 3.51 (m, 2H, CH_2–C*H*$_2$O), 3.80 (s, 3H, PhOC*H*$_3$), 4.44 (s, 2H, OC*H*$_2$–Ph), 6.87 (d, 2H, CH aromatic, $^3J_{HH}$=8.7 Hz), 7.26 (d, 2H, CH aromatic, $^3J_{HH}$=8.7 Hz); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 18.46 (*C*H$_3$–CH), 28.38 (*C*H–CH_3), 34.95 (CH_2–CH_2O), 45.48 (NCH_3), 55.22 (*C*H$_3$OPh), 59.73 (NOCH_3), 67.86 (*C*H$_2$N), 68.24 (CH_2–*C*H$_2$O), 72.46 (Ph–*C*H$_2$O), 113.69 (2CH, aromatic), 129.13 (2CH, aromatic), 130.75 (C, aromatic), 159.03 (*C*OCH$_3$); MS (DCI/NH_3) *m*/*z*: 268 $[MH]^+$.

5.8. 6-(4-(4-Methoxybenzyloxy)-2-methylbutylidene)-2,2,4,4-tetramethylcyclohexane-1,3,5-trione (12)

5.8.1. Mannich base ***11*** synthesis

Aldehyde **9** (0.405 g, 1.822 mmol) in dichloromethane (10 mL) was added to piperidine (180 μL, 1.822 mmol) under argon at room temperature. Syncarpic acid (0.332 g, 1.822 mmol) and piperidine (90 μL, 0.911 mmol) were solubilized in dichloromethane (10 mL). Then, half an hour later, the two solutions were mixed together under argon and stirred for 24 h. After concentration in vacuo, Mannich base **11** was obtained as yellow solid.

5.8.2. Precursor ***12*** synthesis

Mannich base **11** (221 mg, 0.469 mmol) in dichloromethane (10 mL) was treated by saturated NH_4Cl in 1 M HCl solution (10 mL). After 30 min, the aqueous phase was extracted with dichloromethane. Organic phase was washed, dried over $MgSO_4$, filtered and evaporated to give the ene-one **12** as yellow oil (166 mg, 0.430 mmol) in 92% yield, which was immediately engaged in the next step.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (d, 3H, C*H*$_3$–CH, $^3J_{HH}$=6.7 Hz), 1.25 (s, 3H, C*H*$_3$), 1.27 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.77 (m, 2H, C*H*$_2$–CH_2–O), 3.49 (m, 3H, C*H*–CH_3 and CH_2–*C*H$_2$–O), 3.79 (s, 3H, OCH_3), 4.36 (d, 2H, PhC*H*$_2$O), 6.84 (d, 2CH aromatic), 7.20 (d, 2H, 2CH aromatic), 7.30 (d, 1H, C=C*H*, $^3J_{HH}$=10.7 Hz).

5.9. Oxygen uptake

5.9.1. Procedure 1

Ene-one **12** (125 mg, 0.323 mmol) solubilized in dichloromethane was kept under air for 13 days. The mixture was concentrated and then purified. Hydroxy-pyranes **13** (24 mg, 0.060 mmol, 19%) and **14** (22 mg, 0.055 mmol, 17%) and endoperoxides **15**/**16** (15 mg, 0.035 mmol, 11%, 1:1) were separated on silica gel column chromatography (petroleum ether/Et_2O: 3:1 then 1:1).

5.9.2. Procedure 2

Ene-one precursor **12** (230 mg, 0.595 mmol) was solubilized in dichloromethane/methanol 19:1 (80 mL) and then irradiated at 350 nm (Rayonnet) for 2 h 15 min. After evaporation dienol precursor **12′** was kept under air atmosphere at room temperature for

24 h. After removal of the solvents, the crude mixture was purified by column chromatography on silica gel (petroleum ether/AcOEt: 8:2). Hydroxy-pyranes **13** (50 mg, 0.124 mmol, 21%) and **14** (14 mg, 0.035 mmol, 6%) and endoperoxides **15** (22 mg, 0.053 mmol, 9%) and **16** (17 mg, 0.041 mmol, 7%) and hydroperoxide **17** (61 mg, 0.146 mmol, 25%) were separated.

5.9.3. Procedure 3

Ene-one **12** (95 mg, 0.245 mmol) solubilized in dichloromethane/methanol 19:1 (25 mL) was irradiated at 350 nm under argon (Rayonnet) for 1 h 15 min. Rose Bengal (12 mg, 10% weight) was added. The solution was then irradiated in the visible region (Schott Lamp 150 W) under air for 1 h 30 min. The mixture was then concentrated and purified by column chromatography on silica gel (petroleum ether/AcOEt: 8:2). Two diastereoisomers were obtained as uncoloured oil in 34% yield. The *anti* diastereoisomer **15** (20 mg, 0.047 mmol) was obtained in 19% yield and the *syn* diastereoisomer **16** (14 mg, 0.033 mmol) in 14% yield, hydroxy-pyranes **13**/**14** in 27%(1:1) yield and hydroperoxide **17** in 13% yield.

5.9.4. 4-((2R,3R*,4R*)-Tetrahydro-4-hydroxy-2-(4-méthoxyphenyl)-4-methyl-2H-pyran-3-yl)-5-hydroxy-2,2,6,6-tetramethylcyclohex-4-ene-1,3-dione (**13**)*

R_f (petroleum ether/AcOEt: 7:3)=0.08; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.60 (s, 3H, CH_3-9 or 10), 1.17 (s, 3H, CH_3-7 or 8), 1.19 (s, 3H, CH_3-9 or 10), 1.28 (s, 3H, CH_3-21), 1.35 (s, 3H, CH_3-7 or 8), 1.63 and 1.14 (2m, ABX system, 2H, CH_2-13), 3.69 (d, 1H, CH-11, $^3J_{HH}$=11.1 Hz), 3.70 (s, 3H, OCH_3), 4.94 (d, 1H, CH-16, $^3J_{HH}$=11.1 Hz), 4.01 (m, 2H, CH_2-14), 6.72 (d, 2H, CH-19, $^3J_{HH}$=8.7 Hz), 7.17 (d, 2H, CH-18, $^3J_{HH}$=8.7 Hz); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 23.85 (CH_3, C-9 or 10), 24.24 (CH_3, C-7 or 8), 24.63 (CH_3, C-9 or 10), 25.41 (CH_3, C-7 or 8), 28.35 (CH_3, C-21), 40.27 (CH_2, C-13), 47.18 (CH, C-11), 48.47 (C, C-6), 54.27 (C, C-4), 55.32 (OCH_3) 63.92 (CH_2, C-14), 74.91 (CH, C-12), 76.63 (CH, C-16), 109.51 (C, C-2), 113.38 (2CH, C-19), 128.43 (2CH, C-18), 132.30 (C, C-17), 159.60 (C, C-20), 174.43 (C, C-1), 198.29 (C, C-3), 213.55 (C, C-5); IR (diamond compression system) ν 3338 (OH), 2974–2876 (CH aliphatic), 1713 (C=O), 1610, 1518, 1458 (C=C aromatic), 1255 (C–O alcohol), 1064 and 1034 (C–O ether); MS (DCI/NH_3) *m/z*: 403 $[MH]^+$, 420 $[MNH_4]^+$.

5.9.5. 4-((2R,3S*,4R*)-Tetrahydro-4-hydroxy-2-(4-methoxyphenyl)-4-methyl-2H-pyran-3-yl)-5-hydroxy-2,2,6,6-tetramethylcyclohex-4-ene-1,3-dione (**14**)*

R_f (petroleum ether/AcOEt: 7:3)=0.19; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (s, 3H, CH_3-9 or 10), 1.04 (s, 3H, CH_3-7 or 8), 1.21 (s, 3H, CH_3-21), 1.24 (s, 3H, CH_3-9 or 10), 1.32 (s, 3H, CH_3-7 or 8), 1.61 and 1.91 (m, ABX system, 2H, CH_2-13), 3.72 (s, 3H, OCH_3), 3.80 (m, 1H, CH-11), 4.30 (m, 2H, CH_2-14), 5.47 (d, 1H, CH-16, $^3J_{HH}$=3.4 Hz), 6.76 (d, 2H, CH-19, $^3J_{HH}$=8.9 Hz), 7.15 (d, 2H, CH-18, $^3J_{HH}$=8.9 Hz); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 22.75 (CH_3, C-9 or 10), 24.47 (CH_3, C-7 or 8), 25.55 (CH_3, C-7 or 8), 26.41 (CH_3, C-9 or 10), 28.77 (CH_3, C-21), 35.65 (CH_2, C-13), 47.04 (C, C-11), 48.76 (C, C-6), 54.99 (C, C-4), 55.21 (OCH_3), 65.52 (CH_2, C-14), 70.90 (C, C-12), 76.48 (CH, C-16), 108.94 (C, C-2), 113.24 (2CH, C-19), 125.27 (2CH, C-18), 131.08 (C, C-17), 158.59 (C, C-20), 174.28 (C, C-1), 199.42 (C, C-3), 212.96 (C, C-5); IR (diamond compression system) ν 3396 (OH), 3073 (=C–H aromatic), 2978 to 2867 (CH aliphatic), 1711 (C=O), 1613, 1516, 1459 (C=C aromatic), 1253 (C-O alcohol), 1053 and 1036 (C–O ether) cm^{-1}; MS (DCI/NH_3) *m/z*: 403 $[MH]^+$, 420 $[MNH_4]^+$.

5.9.6. (3S,8aR*)-3-(2-(4-Methoxybenzyloxy)ethyl)-8,8a-dihydro-8a-hydroxy-3,6,6,8,8-pentamethylbenzo[c][1,2]dioxine-5,7(3H,6H)-dione (**15**)*

R_f (petroleum ether/AcOEt: 7:3)=0.32; ^{1}H NMR (500 MHz, C_6D_6) δ 0.77 (s, 3H, CH_3-11 or 12), 0.99 (s, 3H, CH_3-15), 1.42 (s, 3H, CH_3-13 or 14), 1.44 (s, 3H, CH_3-13 or 14), 1.48 (s, 3H, CH_3-11 or 12), 1.92 and 2.02 (m, 2H, CH_2CH_2O, ABX system), 3.30 (s, 3H, PhOCH_3), 3.37 (m, 2H, CH_2CH_2O), 4.19 (2d, 2H, OCH_2Ph, $^3J_{HH}$=11.4 Hz), 6.83 (d, 2H, 2CH-21, $^3J_{HH}$=8.7 Hz), 7.15 (s, 1H, C=CH), 7.19 (d, 2H, 2CH-20, $^3J_{HH}$=8.7 Hz); ^{13}C NMR (125.76 MHz, C_6D_6) δ 15.69 (CH_3, C-11 or 12), 20.96 (CH_3, C-11 or 12), 21.27 (CH_3, C-15), 24.46 (CH_3, C-13 or 14), 26.77 (CH_3, C-13 or 14), 37.30 (CH_2, C-16), 51.93 (C, C-10), 54.79 (OCH_3), 55.01 (C, C-8), 65.52 (CH_2, C-17), 72.98 (CH_2, C-18), 80.72 (C, C-4), 97.79 (C, C-1), 114.17 (2CH, C-21), 129.61 (2CH, C-20), 130.63 (C, C-19), 131.99 (C, C-6), 142.46 (CH, C-5), 159.86 (C, C-22), 197.79 (C=O, C-7), 209.87 (C=O, C-9), IR (thin film) ν 3440 (OH), 2979–2872 (CH_2 and CH_3), 1725 (C=O), 1692 (C=O α,β-unsaturated), 1638 (C=C ethylenic), 1608, 1514 (C=C aromatics), 1302 to 1170 (C–O), 1100 (C–O peroxide), 1068 (C–O alcohol) cm^{-1}; MS (IS) *m/z*: 441 $[MNa]^+$; HRMS (IS, MeOH): calculated for $C_{23}H_{30}O_7Na$ 441.1889, found 441.1859.

5.9.7. (3R,8aR*)-3-(2-(4-Methoxybenzyloxy)ethyl)-8,8a-dihydro-8a-hydroxy-3,6,6,8,8-pentamethylbenzo[c][1,2]dioxine-5,7(3H,6H)-dione (**16**)*

R_f (petroleum ether/AcOEt: 7:3)=0.42; ^{1}H NMR (500 MHz, C_6D_6) δ 0.81 (s, 3H, CH_3-11 or 12), 1.15 (s, 3H, CH_3-15), 1.43 (s, 3H, CH_3-13 or 14), 1.44 (m, 2H, CH_2-16), 1.47 (s, 3H, CH_3-13 or 14), 1.55 (s, 3H, CH_3-11 or 12), 3.11 (m, 2H, CH_2CH_2O), 3.25 (s, 3H, PhOCH_3), 4.07 (2d, 2H, OCH_2Ph, $^3J_{HH}$=11.7 Hz), 6.75 (d, 2H, H-21, $^3J_{HH}$=8.7 Hz), 7.03 (s, 1H, C=CH), 7.09 (d, 2H, H-20, $^3J_{HH}$=8.5 Hz); ^{13}C NMR (125.76 MHz, C_6D_6) δ 15.66 (CH_3, C-11 or 12), 20.49 (CH_3, C-11 or 12), 23.53 (CH_3, C-15), 23.90 (CH_3, C-13 or 14), 26.76 (CH_3, C-13 or 14), 36.92 (CH_2, C-16), 51.37 (C, C-10), 54.73 (OCH_3), 55.07 (C, C-8), 65.42 (CH_2, C-17), 72.73 (CH_2, C-18), 80.69 (C, C-4), 97.54 (C, C-1), 114.21 (2CH, C-21), 129.47 (C, C-19), 129.58 (2CH, C-20), 133.35 (C, C-6), 140.46 (CH, C-5), 160.00 (C, C-22), 197.49 (C, C-7), 209.86 (C, C-9); IR (thin film) ν 3440 (OH), 2979–2872 (CH_2 and CH_3), 1724 (C=O), 1692 (C=O, α,β-unsaturated), 1638 (C=C, ethylenic), 1612, 1587, 1514 (C=C, aromatic), 1302–1172 (C–O), 1099 (C–O, peroxide), 1070 (C–O, alcohol) cm^{-1}; MS: (IS) *m/z* 441 $[MNa]^+$; HRMS (IS, MeOH): calculated for $C_{23}H_{30}O_7Na$ 441.1889, found 441.1897.

5.9.8. 4-((2R,3S*,4R*)-Tetrahydro-4-hydroperoxy-2-(4-methoxyphenyl)-4-methyl-2H-pyran-3-yl)-5-hydroxy-2,2,6,6-tetramethylcyclohex-4-ene-1,3-dione (**17**)*

R_f (petroleum ether/AcOEt: 7:3)=0.38; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (s, 3H, CH_3-9 or 10), 1.04 (s, 3H, CH_3-7 or 8), 1.21 (s, 3H, CH_3-21), 1.23 (s, 3H, CH_3-9 or 10), 1.33 (s, 3H, CH_3-7 or 8), 1.98 (m, 2H, CH_2-13), 3.72 (s, 3H, OCH_3), 4.22 (m, 2H, CH_2-14), 4.39 (d, 1H, CH-11, $^3J_{HH}$=3.8 Hz), 5.32 (d, 1H, CH-16, $^3J_{HH}$=3.8 Hz), 6.76 (d, 2H, CH-19, $^3J_{HH}$=8.9 Hz), 7.15 (d, 2H, CH-18, $^3J_{HH}$=8.9 Hz). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 22.36 (CH_3, C-21), 22.58 (CH_3, C-9 or 10), 24.45 (CH_3, C-7 or 8), 25.41 (CH_3, C-7 or 8), 26.33 (CH_3, C-9 or 10), 31.65 (CH_2, C-13), 40.76 (CH, C-11), 48.72 (C, C-6), 54.97 (C, C-4), 55.26 (OCH_3), 65.30 (CH_2, C-14), 76.48 (CH, C-16), 82.33 (C, C-12), 108.26 (C, C-2), 113.33 (2CH, C-19), 125.18 (2CH, C-18), 130.87 (C, C-17), 158.74 (C, C-20), 175.16 (C, C-1), 199.36 (C, C-3), 212.84 (C, C-5); MS (DCI/NH_3) *m/z* 419 $[MH]^+$, 420 $[MNH_4]^+$.

5.10. Methylation of peroxyhemiketal (15) or (16)

Compound *anti* (**15**) or *syn* (**16**) endoperoxide (35 mg, 0.084 mmol) was solubilized in tetrahydrofurane (6 mL) under argon. At −78 °C, butyllithium (1.3 M in hexane) (64 μL, 0.084 mmol) was added and the mixture was stirred for 15 min. Then, methyl triflate (9.5 μL, 0.084 mmol) was introduced. After 4 h at −78 °C, saturated NH_4Cl solution was added. Aqueous phase was extracted with dichloromethane. After washing with water, the organic phase was filtered and dried ($MgSO_4$). Methylated endoperoxide was obtained after purification on silica gel column chromatography

(petroleum ether/AcOEt: 9:1) as uncoloured oil (19 mg, 0.046 mmol) in 52% yield.

5.10.1. (3S,8aR*)-3-(2-(4-Methoxybenzyloxy)ethyl)-8,8a-dihydro-8a-methoxy-3,6,6,8,8-pentamethylbenzo[c][1,2]dioxine-5,7(3H,6H)-dione (**18**)*

R_f (petroleum ether/EtOAc: 7:3)=0.57; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (s, 3H, CH_3-11 or 12), 1.29 (s, 6H, 2CH_3-11 or 12 and 13 or 14), 1.32 (s, 3H, CH_3-13 or 14), 1.35 (s, 3H, CH_3-15), 2.08 (m, 2H, CH_2-16), 3.45 (s, 3H, OMe), 3.61 (m, 2H, CH_2O-17), 3.80 (s, 3H, PhO*Me*), 4.43 (s, 2H, O*C*H_2Ph), 6.87 (d, 2H, 2CH-21, $^3J_{HH}$=8.8 Hz), 7.24 (d, 2H, 2CH-20, $^3J_{HH}$=8.8 Hz), 7.40 (s, 1H, CH-5); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 15.66 (CH_3-11 or 12), 21.23 (CH_3-15), 21.75 (CH_3-11 or 12), 24.81 (CH_3-13 or 14), 25.91 (CH_3-13 or 14), 36.63 (CH_2-16), 53.18 (C-10), 54.47 (C-8), 54.73 (OMe), 55.28 (PhO*Me*), 65.36 (CH_2O-17), 72.86 (O*C*H_2Ph), 80.22 (C-4), 100.38 (C-1), 113.84 (2CH-21), 128.06 (C-6), 129.30 (2CH-20), 130.06 (C-19), 145.44 (CH-5), 159.26 (C-22), 198.85 (C-7), 210.47 (C-9); IR (thin film) ν 2978–2873 (CH_2 and CH_3), 2838 (CH, OMe), 1724 (C=O), 1692 (C=O, α,β-unsaturated), 1636, 1613, 1514 (C=C aromatic), 1298–1173 (C–O), 1101 (C–O peroxide) cm^{-1}; MS (IS, MeOH) *m*/*z*: 455 [MNa]$^+$; HRMS (IS, MeOH): calculated for $C_{24}H_{32}O_7Na$ 455.2046, found 455.2039.

5.10.2. (3R,8aR*)-3-(2-(4-Methoxybenzyloxy)ethyl)-8,8a-dihydro-8a-methoxy-3,6,6,8,8-pentamethylbenzo[c][1,2]dioxine-5,7(3H,6H)-dione (**19**)*

R_f (petroleum ether/EtOAc: 7:3)=0.57; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 3H, CH_3-11 or 12), 1,29 (s, 3H, CH_3-13 or 14), 1.30 (s, 3H, CH_3-11 or 12), 1.34 (s, 3H, CH_3-13 or 14), 1.46 (s, 3H, CH_3-15), 2.01 (t, 2H, CH_2-16), 3.39 (s, 3H, OMe), 3,53 (t, 2H, CH_2O-17), 3.80 (s, 3H, PhO*Me*), 4.40 (s, 2H, C*H*$_2$Ph), 6.87 (d, 2H, 2CH-21, $^3J_{HH}$=8.7 Hz), 7.24 (d, 2H, 2CH-20, $^3J_{HH}$=8.7 Hz), 7.53 (s, 1H, CH-5); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 15.66 (CH_3-11 or 12), 21.73 (CH_3-11 or 12), 22.52 (CH_3-15), 24.80 (CH_3-13 or 14), 25.93 (CH_3-13 or 14), 37.51 (CH_2-16), 53.29 (C-10), 54.47 (OMe), 54.73 (C-8), 55.28 (PhO*Me*), 64.76 (CH_2O-17), 72.91 (O*C*H_2Ph), 80.30 (C-4), 100.52 (C-1), 113.85 (2CH-21), 128.06 (C-6), 129.35 (2CH-20), 129.88 (C-19), 145.67 (CH-5), 159.29 (C-22), 198.60 (C-7), 210.48 (C-9); IR (thin film) ν 2977–2866 (CH_2 and CH_3), 2836 (CH, OMe), 1725 (C=O), 1691 (C=O, α,β-unsaturated), 1636, 1613, 1514 (C=C aromatics), 1302–1173 (C–O), 1101 (C–O peroxide) cm^{-1}; MS (IS, MeOH) *m*/*z*: 455 [MNa]$^+$; HRMS (IS, MeOH): calculated for $C_{24}H_{32}O_7Na$ 455.2046, found 455.2035.

5.11. Deprotection of PMB

Methylated endoperoxide (19 mg, 0.044 mmol) was dissolved in dichloromethane (4.5 mL). Water (0.25 mL) was added and then dichlorodicyanobenzoquinone (12 mg, 0.053 mmol) at room temperature. After 5 h, saturated $NaHCO_3$ solution was poured on crude mixture, which was extracted by ethyl acetate. Organic phase was washed with water and then brine. After drying on magnesium sulfate, filtering and concentrating, hydroxyl-endoperoxide was obtained as uncoloured oil in quantitative yield.

5.11.1. (3R,8aS*)-8,8a-Dihydro-3-(2-hydroxyethyl)-8a-methoxy-3,6,6,8,8-pentamethylbenzo[c][1,2]dioxine-5,7(3H,6H)-dione (**20**)*

See Ref. 16.

5.11.2. (3R,8aR*)-8,8a-Dihydro-3-(2-hydroxyethyl)-8a-methoxy-3,6,6,8,8-pentamethylbenzo[c][1,2]dioxine-5,7(3H,6H)-dione (**21**)*

R_f (petroleum ether/EtOAc: 7:3)=0.17; ^{1}H NMR (500 MHz, C_6D_6) δ 0.79 (s, 3H, CH_3-11 or 12), 1.15 (s, 3H, CH_3-15), 1.38 (s, 3H, CH_3-13 or 14), 1.42 (s, 3H, CH_3-13 or 14), 1.55 (s, 3H, CH_3-11 or 12), 1.68 (m, 2H, CH_2), 3.20 (m, 2H, C*H*$_2$–OH), 3.24 (s, 3H, OCH_3), 7.50 (s, 1H, C=C*H*); ^{13}C NMR (125.77 MHz, C_6D_6) δ 16.16 (CH_3-11 or 12), 21.67 (CH_3-11 or 12), 22.49 (CH_3-15), 26.04 (CH_3-13 or 14), 26.22 (CH_3-13 or 14), 37.67 (CH_2), 53.29 (C-10), 54.33 (OCH_3), 54.66 (C-8), 64.89 (CH_2OH), 80.24 (C-4), 101.01 (C-1), 128.38 (C-6), 145.69 (CH-5), 198.08 (C-7), 209.48 (C-9); IR (neat) ν 3450 (OH), 2924–2854 (CH_2 and CH_3), 1723 (C=O), 1691 (C=O, α,β-unsaturated), 1631 (C=C), 1260 (C–O), 1100 (C–O–O–C) cm^{-1}; MS (IS, MeOH) *m*/*z*: 335 [MNa]$^+$; HRMS (IS, MeOH): calculated for $C_{16}H_{24}O_6Na$ 335.1471, found 335.1467.

5.12. 4-((2*R**,3*S**,4*R**)-Tetrahydro-4-hydroperoxy-2-(4-methoxyphenyl)-4-methyl-2*H*-pyran-3-yl)-5-hydroxy-2,2,6,6-tetramethylcyclohex-4-ene-1,3-dione (22)

Hydroperoxide **17** (66 mg, 0.157 mmol) was solubilized in anhydrous THF (15 mL) under argon. At −78 °C, BuLi (1.3 M/hexane) (121 μL, 0.157 mmol) was added dropwise and the solution was stirred for 15 min. Then, methyl triflate (18 μL, 0.157 mmol) was added and the solution stirred for 4 h at −78 °C. Reaction was quenched with saturated NH_4Cl solution. Extraction was performed with dichloromethane. Organic phase was washed with water, dried over $MgSO_4$, filtered and evaporated. Crude mixture was purified on silica gel column chromatography (petroleum ether/EtOAc: 9:1) to furnish methyl peroxide **22** as a white solid (27 mg, 0.062 mmol, 40%).

R_f (petroleum ether/EtOAc: 7:3)=0.58; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (s, 3H, CH_3-9 or 10), 1.03 (s, 3H, CH_3-7 or 8), 1.19 (s, 3H, CH_3-21), 1.23 (s, 3H, CH_3-9 or 10), 1.32 (s, 3H, CH_3-7 or 8), 1.90 (m, 2H, CH_2-13), 3.72 (s, 3H, PhO*Me*), 3.91 (s, 3H, $OOCH_3$), 4.20 (m, 2H, CH_2-14), 4.35 (d, 1H, CH-11, $^3J_{HH}$=3.8 Hz), 5.31 (d, 1H, CH-16, $^3J_{HH}$=3.8 Hz), 6.75 (d, 2H, CH-19, $^3J_{HH}$=8.9 Hz), 7.15 (d, 2H, CH-18, $^3J_{HH}$=8.9 Hz); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 22.66 (CH_3, C-9 or 10), 22.77 (CH_3, C-21), 24.41 (CH_3, C-7 or 8), 25.41 (CH_3, C-7 or 8), 26.21 (CH_3, C-9 or 10), 32.10 (CH_2, C-13), 40.97 (CH, C-11), 48.68 (C, C-6), 54.96 (C, C-4), 55.25 (PhOCH_3), 63.34 ($OOCH_3$), 65.31 (CH_2, C-14), 76.55 (CH, C-16), 81.83 (C, C-12), 108.19 (C, C-2), 113.29 (2CH, C-19), 125.20 (2CH, C-18), 130.98 (C, C-17), 158.64 (C, C-20), 175.52 (C, C-1), 198.82 (C, C-3), 213.12 (C, C-5); IR (diamond compression system) ν 2996 (CH_3 peroxide), 2977–2891 (CH aliphatic), 1713 (C=O), 1639 (C=O, α,β-unsaturated), 1597, 1515, 1460 (C=C, aromatic), 1249, 1085 and 1048 (C–O ether) cm^{-1}; MS: (DCI/NH_3) *m*/*z*: 433[MH$^+$]; HRMS (IS, MeOH): calculated for $C_{24}H_{33}O_7$ 433.2226, found 433.2245.

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References and notes

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22. Crystal data for **13**: $C_{23}H_{30}O_6$, M=402.47, orthorhombic, space group $P2_12_12_1$, a=9.4105(8) Å, b=12.4752(10) Å, c=18.3094(15) Å, V=2149.5(3) Å^3, Z=4, crystal size 0.30×0.20×0.15 mm^3, 13,140 reflections collected (3052 independent, R_{int}=0.0586), 270 parameters, R_1 [$I>2\sigma(I)$]=0.0347, wR_2 [all data]=0.0747, largest diff. peak and hole: 0.148 and −0.128 e Å^{-3}.
Crystal data for **14**: $C_{23}H_{30}O_6$, M=402.47, monoclinic, space group $C2/c$, a=27.226(2) Å, b=17.7789(14) Å, c=9.4816(8) Å, β=107.9940(10)°, V=4365.1(6) Å^3, Z=8, crystal size 0.20×0.15×0.10 mm^3, 13,086 reflections collected (3092 independent, R_{int}=0.0602), 270 parameters, R_1 [$I>2\sigma(I)$]=0.0477, wR_2 [all data]=0.1142, largest diff. peak and hole: 0.250 and −0.164 e Å^{-3}.
Crystal data for **17**: $C_{23}H_{30}O_7$, M=418.47, triclinic, space group $P\bar{1}$, a=9.0594(10) Å, b=10.0918(11) Å, c=11.9515(13) Å, α=82.985(2)°, β=86.242(2)°, γ=85.038(2)°, V=1078.8(2) Å^3, Z=2, crystal size 0.30×0.30×0.20 mm^3, 8527 reflections collected (4294 independent, R_{int}=0.0320), 374 parameters, $R_1[I>2\sigma(I)]$=0.0495, $wR2$ [all data]=0.1376, largest diff. peak and hole: 0.297 and −0.156 e Å^{-3}. Crystal data for **22**: $C_{24}H_{32}O_6$, M=432.57, orthorhombic, space group $Fdd2$, a=16.6546(5) Å, b=65.3587(17) Å, c=8.1613(2) Å, V=8883.8(4) Å^3, Z=16, crystal size 0.40×0.20×0.10 mm^3, 20,376 reflections collected (3627 independent, R_{int}=0.0666), 310 parameters, R_1 [$I>2\sigma(I)$]=0.0436, wR_2 [all data]=0.0917, largest diff. peak and hole: 0.175 and −0.156 e Å^{-3}. Data for all structures were collected at 173(2) K using an oil-coated shock-cooled crystal on a Bruker-AXS APEX II diffractometer (λ=0.71073 Å). Semi-empirical absorption corrections were employed for **13**, **14**, **17** and **22**.[23] The structures were solved by direct methods (SHELXS-97),[24] and refined using the least-squares method on F^2.[25] Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-689774 (**13**), CCDC-689775 (**14**), CCDC-689776 (**17**) and CCDC-689777 (**22**). These data can be obtained free of charge via www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk).
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