Tetrahedron 65 (2009) 7372–7379

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

α-Spiro endoperoxides: synthesis and evaluation of their antimalarial activities

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ARTICLE INFO

Article history:
Received 12 May 2009
Received in revised form 7 July 2009
Accepted 9 July 2009
Available online 14 July 2009

ABSTRACT

Endoperoxides belonging to the G-factor family, containing a spiroalkane moiety in the α position to the O–O bond, have been synthesized via an autoxidation reaction on the corresponding dienol precursors. Methylated derivatives in the peroxyhemiketal position have also been prepared. The in vitro antimalarial activities are reported. Fe(II)-induced reduction on endoperoxides **8** and **9** have been studied.

1. Introduction

Malaria is a major health problem in tropical and subtropical regions, causing more than one million deaths each year. Since malaria parasites are developing resistance to drugs such as chloroquine, new antiparasitic drugs are urgently required at an affordable price.[1] The search for a new generation of artemisinin-based therapeutics is being pursued.[2] Synthetic peroxide-containing compounds such as 1,2,4-trioxanes,[3] 1,2,4-trioxolanes,[4] cyclic peroxyketals,[5] and endoperoxides[6] have also been developed targeting *Plasmodium falciparum*.

We are interested in antimalarial agents acting in the same way as artemisinin and we focused on the synthesis of new endoperoxides, related to the natural phytohormones known as G-factors (G1, G2, G3)[7] (Fig. 1). These natural bicyclic endoperoxides contribute to frost and hydric stress resistance in *Eucalyptus* and *Myrtaceae* species. Some of the previously synthesized compounds present moderate to potent antimalarial activity.[8]

Alkylation of the peroxyhemiketal function proved to be crucial for activity.[9] Benzyl ether analogues (G3Bn) exhibited the highest activities (IC_{50}=300 and 100 nM on chloroquine sensitive and resistant strains of *P. falciparum*, respectively). Both enantiomers displayed similar activity, which was approximately three-fold better than the methylated ether analogue. Studies concerning Fe(II)-induced reduction of the O–O bond[10] revealed that, after a single electron transfer from Fe(II) to the O–O bond, the homolytic cleavage of the peroxidic function led in majority to the products following route (a). Thus, after formation of the O1 centered radical, it quickly rearranges to tertiary *gem* dimethyl C-centered radical (Scheme 1). This tertiary radical evolves differently depending alkylation or substitution of the peroxyhemiketal function.

In our search for new antimalarial endoperoxides related to the G-factor family, we decided to prepare α-spiro endoperoxides in

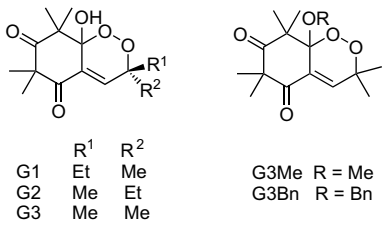
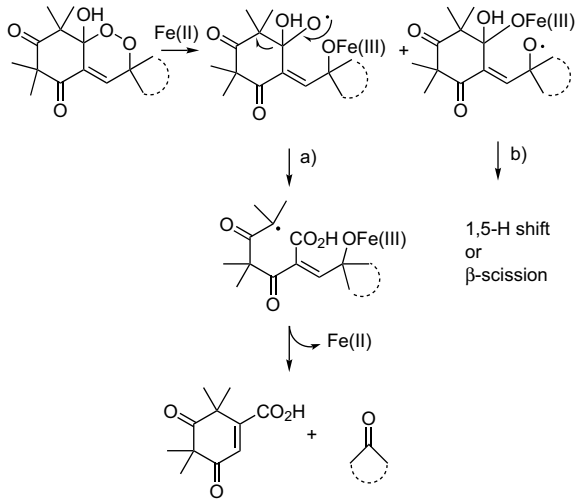


Figure 1. G-factors and functionalized endoperoxides.



Scheme 1. Hypothesis of Fe(II)-induced reduction on spiro-endoperoxides.

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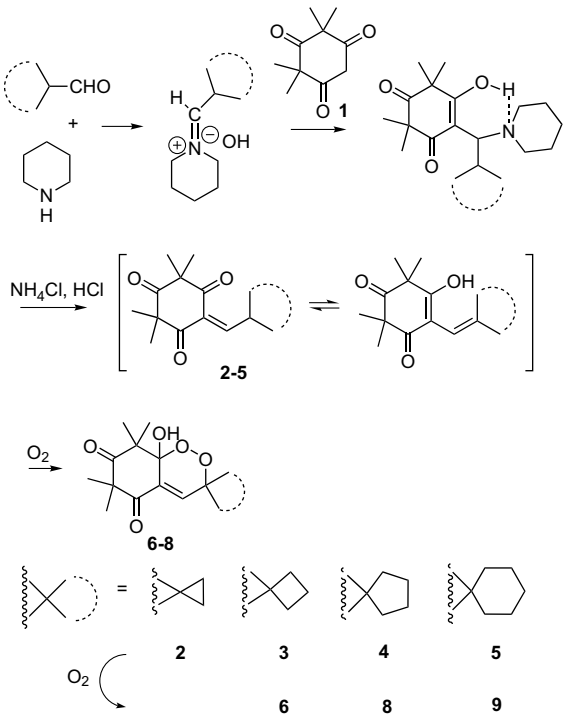
0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.07.030

order to explore the possibility of Fe(II)-induced reduction leading to homolytic cleavage of the peroxo linkage following the competitive route (b). The O2-centered radical may then be formed and rearranged to the primary C-centered radical, either via β-scission or via a secondary C-centered radical followed by a 1,5-H shift (Scheme 1). In this respect, we were first interested in synthesis of an α-cyclopropyl endoperoxide derivative, which should furnish a primary C-centered radical after Fe(II) induced reduction. Variation of the ring size and use of more elaborated aldehydes, such as norbornene-carboxaldehyde, or protected glyceraldehyde to form an epoxide in α-position of O–O bond, was also considered. The expeditious synthetic strategy planned to prepare these target compounds was based on autoxidation as the key step. We previously showed that spontaneous oxygen uptake proceeded via addition of $^3O_2$ on the dienol, thereby yielding a triplet biradical intermediate characterized by EPR.[11] This work concerns synthesis of such endoperoxides following this methodology,[7] synthesis of their methylated analogues, and evaluation of their antiplasmodial activities.

2. Results and discussion

Synthesis of 2-alkylidene *cyclo*-1,3,5-trione precursors was achieved by a Knoevenagel-type reaction. They were prepared, as previously described,[7] via their Mannich bases to minimize Michael bis-adduct formation. Mannich bases were easily obtained by addition of iminium salts, formed by reaction of piperidine with various aldehydes, on syncarpic acid (**1**). Then, acidic treatment led to precursors (**2**–**5**), which were subsequently submitted to autoxidation (Scheme 2).

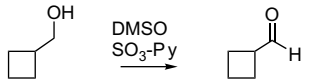


Scheme 2. Synthetic route to α-spiro-alkane-endoperoxides.

2.1. From cycloalkane-carboxaldehydes

Unfortunately, in the case of the cyclopropane-derivative, an endoperoxide could not be obtained. Precursor **2** exists only in the enone form and could not be enolized, not by photo-activation nor by acidic or basic treatment. Consequently, neither auto-oxidation nor photo-oxygenation (via singlet oxygen) could lead to the desired endoperoxide intermediate.

Importantly, α-spiro cyclobutane endoperoxide **6** was successfully prepared although in poor yield (13%). It required the preparation of aldehyde **7** through the Parikh–Doëring oxidation (DMSO, SO_3–pyridine) of hydroxymethyl cyclobutane (Scheme 3). The volatile aldehyde was not purified, but was used directly for condensation with syncarpic acid. The product, **3**, was found to exist exclusively in the enone form; no sign of dienol could be detected by ^{1}H NMR. The autoxidation rate was very slow; even after 6 days enone **3** was still present. In this case, it seems that autoxidation was not selective. Purification by silicagel column chromatography afforded endoperoxide **6** besides enone **3** and several by-products, which were not identified. Endoperoxides **8** and **9** were readily obtained in 85% and 87% yields, respectively, calculated on the three steps. The structure of endoperoxide **8** has been confirmed by X-ray diffraction of the crystals obtained (Fig. 2).



Scheme 3. Preparation of aldehyde **7** via Parikh–Doering oxidation.

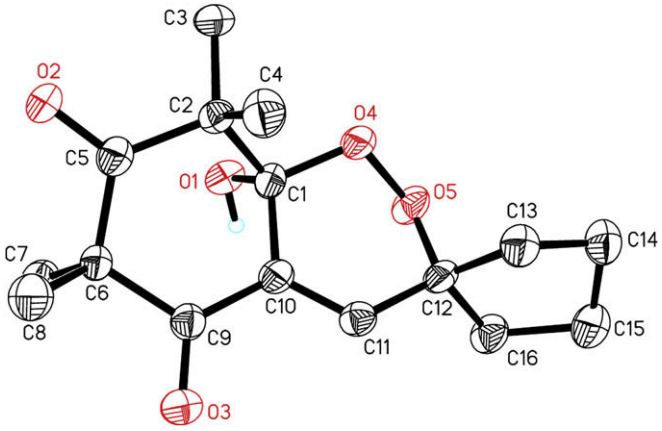


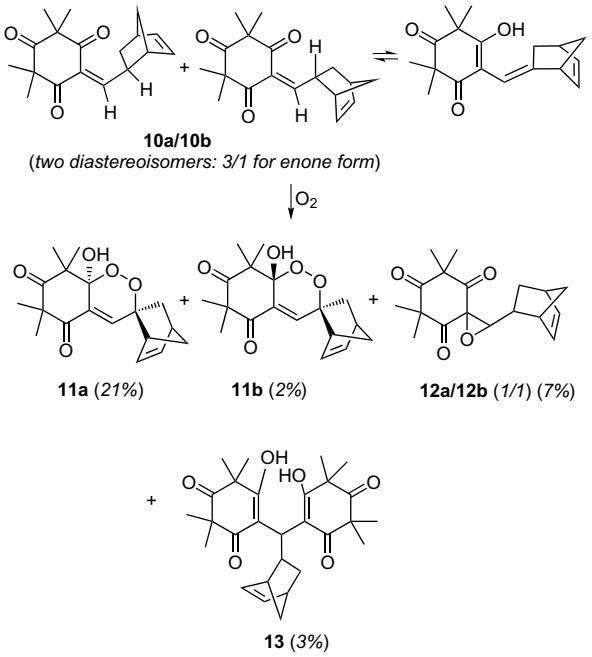
Figure 2. Molecular view of endoperoxide **8** in the solid state (thermal ellipsoids at 50% probability; hydrogen atoms are omitted for clarity).

2.2. From 5-norbornene-2-carboxaldehyde

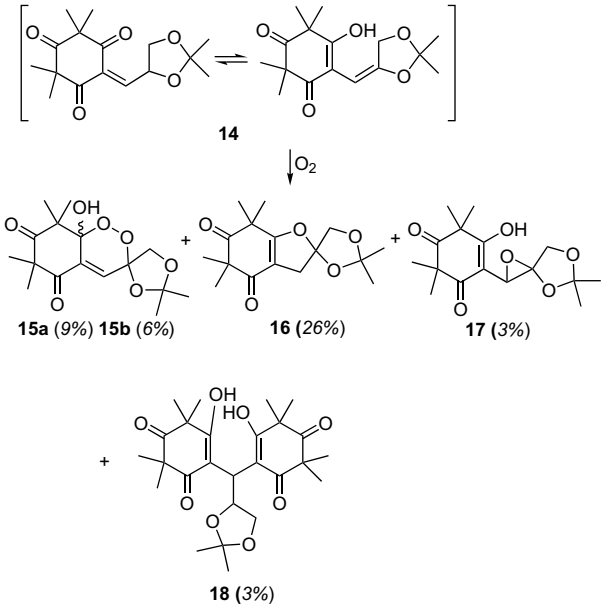
The precursor formed from 5-norbornene-2-carboxaldehyde (*endo*/*exo* 80:20 mixture) and syncarpic acid was obtained as a mixture of two diastereoisomeric enones **10a**/**10b** (75:25) and bis-adduct **13** (<10%). Oxygen uptake revealed to be non-chemoselective: a complex mixture was obtained and purification by silicagel column chromatography afforded two diastereoisomeric endoperoxides in 22% and 2% yield as well as two inseparable diastereoisomeric epoxides **12a**/**12b** (7%), and bis-adduct **13** (3%). An unidentifiable polar byproduct, presumably a polymer, was also observed (Scheme 4).

2.3. From 2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde

As shown in Scheme 5, oxygen uptake on enone **14** afforded a complex mixture. Compounds were separated by chromatography: the major fraction was composed of compound **16** (26%), which resulted from intramolecular addition of dienol-OH on enol ether, in a mixture with endoperoxide **15a** (9%). Endoperoxide **15b** (6%), epoxide **17** (3%), and bis-adduct **18** (3%) could be separated



Scheme 4. Synthetic route starting from norbornene-carboxaldehyde.

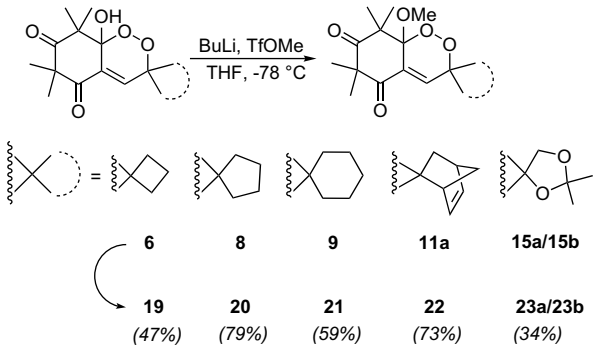


Scheme 5. Synthetic route starting from 2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde.

and identified by 2D NMR and mass spectroscopy. A polar fraction could not be identified.

2.4. Methylation of endoperoxides

As we have shown earlier, the methylation of the peroxyhemiketal function is crucial for antimalarial activity.[9] We planned to methylate the synthesized endoperoxides using previously optimized methodology. Endoperoxides **6**, **8**, **9**, **11a**, **15a**, and **15b** were treated with BuLi in THF at low temperature and the resulting lithium alkoxides were trapped with methyl trifluoromethane sulfonate (Scheme 6) to afford the corresponding methoxy derivatives **19**, **20**, **21**, **22**, **23a**, and **23b**, in moderate to good yield.



Scheme 6. Methylation of the peroxyhemiketal function.

X-ray diffraction analysis was performed on crystals of endoperoxide **22**.[12] It allowed determination of relative configurations of asymmetric carbons and the structure is shown in Figure 3.

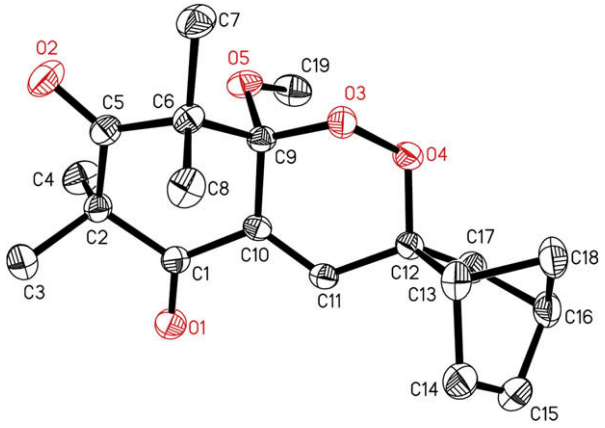


Figure 3. Molecular view of endoperoxide **22** in the solid state (thermal ellipsoids at 50% probability; hydrogen atoms are omitted for clarity).

Endoperoxides **23a** and **23b** were characterized by 2D NMR (HMBC, HSQC experiments). NOESY NMR analysis permitted to differentiate between both diastereoisomeric endoperoxides and their relative stereochemistries (Fig. 4). For endoperoxide **23a**, a correlation spot appeared on NOESY spectrum, between the methoxy and CH_2O whereas no such correlation exists for **23b**. So **23a** was the *anti* diasteroisomer (OMe and CH_2O on the same side) and **23b** the *syn* one. This relative configuration was confirmed by X-ray diffraction analysis of crystals of **23a** (Fig. 5).[12]

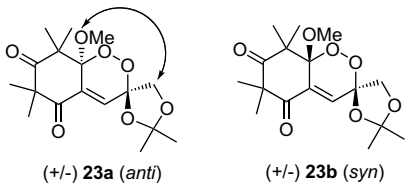


Figure 4. NOE experiments on **23a** and **23b** endoperoxides.

The choice of 2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde was taken to introduce a spiro epoxide in the α-position of the peroxide moiety. Thus, after deprotection of the acetonide, introduction of a leaving group on primary hydroxyl group and nucleophilic ring closure would give the desired epoxide. Unfortunately, the low yield of endoperoxides **23a** and **23b** made it impractical to pursue our initial goals of conversion of the spiro endoperoxide dioxolane into a spiro epoxy endoperoxide.

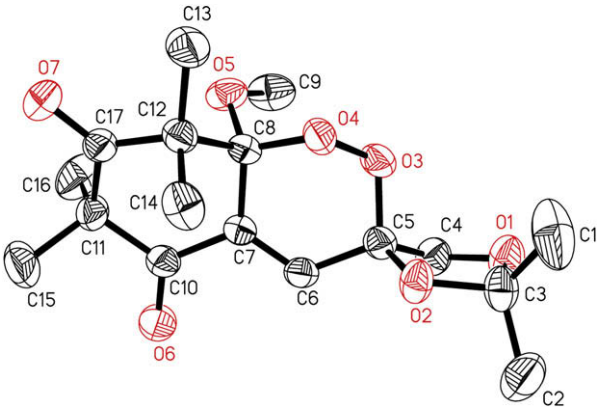


Figure 5. Molecular view of endoperoxide **23a** in the solid state (thermal ellipsoids at 50% probability; hydrogen atoms are omitted for clarity).

3. Antiplasmodial activity

Endoperoxides **6**, **8**, **9**, **11a**, and **15b** and their methylated analogues **19**, **20**, **21**, **22**, **23a**, and **23b** were tested in vitro against the Nigerian strain of *P. falciparum* (Table 1). The activity was determined by Desjardins et al.[16] using [^{3}H] hypoxanthine incorporation to assess parasite growth. Parasitic viability was expressed as IC_{50}, the drug concentration causing 50% parasite growth inhibition.

Table 1
IC_{50} values of several endoperoxides and artemisinin (ART) on Nigerian strains of *Plasmodium falciparum*

	6	**8**	**9**	**11a**	**15a**	**15b**	**G3**	
IC_{50} (μM)	49	56	52	>100	nd[a]	43	30	
	19	**20**	**21**	**22**	**23a**	**23b**	**G3Me**	**ART**
IC_{50} (μM)	4.2	5.5	1.9	50	32	41	0.28	0.015

[a] Not determined.

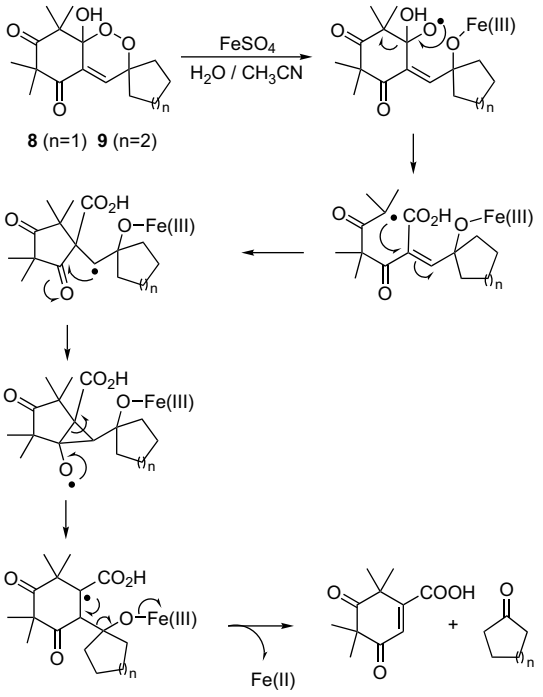
IC_{50} values of non-methylated endoperoxides are in the same range as that of **G3** and present very low inhibition of *Plasmodium* growth. Fe(II) induced reduction was performed on endoperoxides **8** and **9**. The main products were cyclopentyl (hexyl) ketone and the acid previously obtained during Fe(II) reduction of G3 (Scheme 7). As for G3 reduction, only route (a) is involved and the same Fe(II) induced degradation mechanism can be invoked. Methylation of the peroxyhemiketal **6**, **8**, and **9** increases their antimalarial activity from 10- to 30-fold. Nevertheless **G3Me** remains the lead compound with its potent in vitro antimalarial activity in the submicromolar range.

However, the mechanism seems to be quite different for norbornene endoperoxide **11a** and its methylated analogue **22**, which shows no activity at all. Intermediate radicals must add to the double bond.

Concerning dioxolane endoperoxides **15a**/**b** or **23a**/**b**, they probably get deprotected in the acidic digestive vacuole of the parasite (pH=4.5–5.0),[17] which confers a high hydrophilicity and explains the low activity in both cases.

4. Conclusions

An expeditious methodology allowed an easy access to α-spiroalkane endoperoxides with good yields for cyclopentane **8** or cyclohexane **9** and moderate for cyclobutane **6**. In the case of norbornyl or dioxolanyl units, autoxidation led to endoperoxides but in competition with parallel side-reactions. Biological activities of these endoperoxides and their methylated analogues didn't allow lowering IC_{50} values to that obtained for G3Me. The same mode of action as G3Me can be invoked for **20** and **21** and the postulated route (b) wasn't observed.



Scheme 7. Fe(II)-induced reduction of endoperoxide **8** and **9**.

5. Experimental section

5.1. General

Melting points were measured on a Büchi and were uncorrected. The NMR spectra were recorded on a Bruker Avance 300 FT-NMR or Bruker Avance 400. LRMS data were obtained by DCI/NH_3 on a TSQ 7000 Thermo-electron, 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 have been defined using ChemDraw Ultra 8.0 (Cambridge Soft/Chem. Office 2004) software, which determines IUPAC nomenclature. Oxidation precursors **3**–**5**, **10**, and **14** were not described as they were unstable. Only ^{1}NMR spectra were performed.

5.2. 6-(Cyclopropylmethylene)-2,2,4,4-tetramethylcyclohexane-1,3,5-trione (2)

Cyclopropane carboxaldehyde (215 μL, 2.85 mmol) was solubilized in anhydrous dichloromethane (5 mL) at room temperature, under argon. Piperidine (285 μL, 2.85 mmol) was added dropwise. Syncarpic acid (0.519 g, 2.85 mmol) was suspended in dichloromethane (5 mL) and piperidine (141 μL, 1.43 mmol) added dropwise. After 15 min, the iminium solution was poured onto the syncarpic acid suspension. The mixture was left 24 h then concentrated. Mannich base was obtained as a white solid. It was solubilized in dichloromethane, and then treated with saturated NH_4Cl in HCl 1 M solution. The biphasic mixture was stirred for 30 min, separated and the aqueous phase extracted with dichloromethane. Organic phases were brought together, washed, and then dried over magnesium sulfate, filtered then concentrated. Enone **2** (0.638 g, 2.72 mmol) was obtained in 96% yield as a white solid. R_f (pet. ether/AcOEt 9:1) 0.50. ^{1}H NMR (300 MHz, $CDCl_3$)

δ=1.00 (m, 2H, ABX system, CH_2), 1.33 (s, 6H, $2CH_3$), 1.34 (m, 2H, ABX system), 1.35 (s, 6H, $2CH_3$), 2.95 (m, 1H, CH), 6.79 (d, 1H, C=CH, $^3J_{HH}$=11.8 Hz) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$) δ=13.2 (CH_2), 15.3 (CH), 22.5, 22.6 ($2CH_3$), 57.3, 58.4 (2C, $2CH_3CCH_3$), 130.1 (C, *C*=CH), 167.0 (CH, C=*C*H), 196.6, 199.5 (2C, *C*=O), 209.3 (C, C=C–*C*=O) ppm. IR (KBr) ν: 3073 (=CH), 2986–2871 (CH, CH_2 and CH_3), 1716 (C=O), 1585 (C=C) cm^{-1}. MS (DCI/NH_3, CH_2Cl_2, positive mode, *m*/*z*): 252 $[MNH_4]^+$, 269 $[MN_2H_7]^+$. HRMS (ESI, MeOH/HCOOH, positive mode, *m*/*z*): calculated for $C_{14}H_{19}O_3$ 235.1334, found 235.1347.

5.3. Cyclobutane carboxaldehyde 7

Hydroxymethylcyclobutane (219 mg, 2.543 mmol) was solubilized in anhydrous dichloromethane (1.6 mL/mmol) under argon. DMSO (2 mL/mmol), triethylamine (1.767 mL, 12.713 mmol), and SO_3–pyridine complex (2.023 g, 12.713 mmol) were added successively. After 30 min at room temperature, the mixture was diluted in diethyl ether then treated with brine. The organic phase is dried over magnesium sulfate, filtered, and then concentrated. The aldehyde is obtained and used as such. The aldehyde was kept in solution since it is very volatile. ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.70 and 2.36 (m, two parts of ABX systems, 6H, $3CH_2$), 3.17 (m, 1H, CH), 9.72 (d, 1H, C*H*O, $^3J_{HH}$=2.0 Hz) ppm.

5.4. 3-Cyclobutyl-8,8a-dihydro-8a-hydroxy-6,6,8,8-tetramethylbenzo[*c*][1,2]dioxine-5,7(3*H*,6*H*)-dione (6)

Cyclobutane carboxaldehyde (215 μL, 2.85 mmol) was solubilized in anhydrous dichloromethane (13 mL) at room temperature, under argon. Piperidine (252 μL, 2.543 mmol) was added dropwise. Syncarpic acid (368 mg, 2.020 mmol) was suspended in dichloromethane (13 mL) and piperidine (201 μL, 2.034 mmol) added dropwise. After 15 min the iminium solution was poured on the syncarpic acid suspension. The mixture was left 30 min and then concentrated. The Mannich base was obtained as a white solid. It was solubilized in dichloromethane, and then treated by saturated NH_4Cl in HCl 1 M solution. The biphasic mixture was stirred for 30 min, and then the aqueous phase extracted with dichloromethane. Organic phases were brought together, washed, and then dried over magnesium sulfate, filtered, and then concentrated. Enone was left under air for 6 days. After evaporation and purification of the raw mixture by silicagel column chromatography (pet. ether/AcOEt 9:1) endoperoxide **6** (74 mg, 0.264 mmol) was obtained as white solid in 13% yield (calculated on three steps from syncarpic acid). R_f (pet. ether/AcOEt 8:2) 0.28. ^{1}H NMR (300 MHz, $CDCl_3$) δ=0.99, 1.31, 1.36, 1.37 (4s, 3H, $4CH_3$), 1.81, 2.66 (m, 6H, ABX_2 system, $3CH_2$), 3.68 (1H, OH), 7.43 (s, 1H, C=CH) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$) δ=12.9 (CH_2), 15.1, 20.8, 24.0, 26.6 ($4CH_3$), 30.8, 32.6 ($2CH_2$), 51.7, 54.9 (2C, $2CH_3CCH_3$), 81.9 (C, C=C–*C*O), 97.5 (C, *C*O(OH)), 131.3 (C, *C*=CH), 140.2 (CH, C=*C*H), 198.2 (C, C=C–*C*=O), 210.6 (C, *C*=O) ppm. IR (KBr) ν: 3441 (OH), 2980–2870 (CH_2 and CH_3), 1722 (C=O), 1690 (α,β unsaturated C=O), 1633 (C=C), 1101 (C–O peroxide), 1065 (C–O) cm^{-1}. MS (ESI, MeOH, positive mode, *m*/*z*): 303 $[MNa]^+$, 583 $[2MNa]^+$. HRMS (ESI, orthophosphoric acid, positive mode, *m*/*z*): calculated for $C_{15}H_{21}O_5$ 281.1389, found 281.1430.

5.5. 3-Cyclopentyl-8,8a-dihydro-8a-hydroxy-6,6,8,8-tetramethylbenzo[*c*][1,2]dioxine-5,7(3*H*,6*H*)-dione (8)

The procedure was the same as that previously described but using cyclopentanecarboxaldehyde (300 mg, 3.057 mmol) and syncarpic acid (557 mg, 3.057 mmol). Enone was kept under air for 24 h. After purification by silicagel column chromatography (pet. ether/AcOEt 9:1), endoperoxide **8** (768 mg, 2.609 mmol) was obtained in 85% yield as a white solid. R_f (pet. ether/AcOEt 8:2) 0.37. ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.03, 1.31, 1.36, 1.38 (4s, 3H, $4CH_3$), 1.60, 2.40 (m, 8H, $4CH_2$), 3.62 (1H, O*H*), 7.19 (s, 1H, C=C*H*) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$) δ=15.1, 21.0, 24.1, 26.6 ($4CH_3$), 24.5, 24.9 ($2CH_2$), 35.6, 36.1 ($2CH_2$), 51.6, 54.9 (2C, $2CH_3CCH_3$), 90.4 (C, C=C–*C*O), 97.6 (C, *C*O(OH)), 131.8 (C, *C*=CH), 142.7 (CH, C=*C*H), 198.1 (C, C=C–*C*=O), 210.7 (C, *C*=O) ppm. IR (diamond compression system) ν: 3430 (OH), 3061 (=CH), 2974–2868 (CH_2 and CH_3), 1721 (C=O), 1687 (α,β unsaturated C=O), 1637 (C=C), 1096 (C–O peroxide), 1086 (C–O alcohol) cm^{-1}. MS (ESI, MeOH, positive mode, *m*/*z*): 317 $[MNa]^+$, 611 $[2MNa]^+$. HRMS (ESI, MeOH, positive mode, *m*/*z*): calculated for $C_{16}H_{22}O_5Na$ 317.1365, found 317.1309. Mp (Büchi)=129 °C.

5.6. 3-Cyclohexyl-8,8a-dihydro-8a-hydroxy-6,6,8,8-tetramethylbenzo[*c*][1,2]dioxine-5,7(3*H*,6*H*)-dione (9)

The procedure was the same as that previously described but using cyclohexanecarboxaldehyde (194 mg, 1.730 mmol) and syncarpic acid (300 mg, 1.646 mmol). Enone was kept under air for 24 h. After purification by silicagel column chromatography (EP/AcOEt 9:1), endoperoxide **9** (768 mg, 2.609 mmol) was obtained in 87% yield as a white solid. R_f (pet. ether/AcOEt 8:2) 0.31. ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.04, 1.32, 1.36, 1.37 (4s, 3H, $4CH_3$), 1.50, 2.02 (m, 10H, $5CH_2$), 3.72 (s, 1H, O*H*), 7.18 (s, 1H, C=C*H*) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$) δ=15.1, 21.0, 24.1, 26.6 ($4CH_3$), 20.9, 21.1, 25.0, 31.7–33.0 ($5CH_2$), 51.6, 54.9 (2C, $2CH_3CCH_3$), 80.6 (C, C=C–*C*O), 97.6 (C, *C*O(OH)), 132.0 (C, *C*=CH), 142.8 (CH, C=*C*H), 198.4 (C, C=C–*C*=O), 210.7 (C, *C*=O) ppm. IR (diamond compression system) ν: 3455 (OH), 3059 (=CH), 2997–2848 (CH_2 and CH_3), 1714 (C=O), 1687 (α,β unsaturated C=O), 1635 (C=C), 1092 (C–O peroxide), 1065 (C–O alcohol) cm^{-1}. MS (ESI, MeOH, positive mode, *m*/*z*): 331 $[MNa]^+$, $[2MNa]^+$. HRMS (ESI, MeOH, positive mode, *m*/*z*): calculated for $C_{17}H_{24}O_5Na$ 331.1521, found 331.1588; calculated for $C_{34}H_{48}O10_5Na$ 639.3145, found 639.3187. Mp (Büchi)=124 °C.

5.7. Synthesis of endoperoxides 11a and 11b

The procedure was the same as that previously described but using 5-norbornene-2-carboxaldehyde (362 mg, 2.964 mmol) and syncarpic acid (540 mg, 2.964 mmol). Enone was kept under air for 3 days. After purification by silicagel column chromatography (pet. ether/AcOEt 9:1), two diastereoisomeric endoperoxides **11a** (209 mg, 0.656 mmol, 21%) and **11b** (20 mg, 0.063 mmol, 2%) were obtained as a white solids besides a mixture 1:1 of two diastereoisomeric epoxides **12a**/**b** (66 mg, 0.218 mmol, 7%) and Michael adduct **13** (42 mg, 0.090 mmol, 3%).

*5.7.1. Diastereoisomer **11a***

R_f (pet. ether/AcOEt 8:2) 0.35. ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.09, 1.34, 1.37 (4s, 3H, 3H, 6H, $4CH_3$), 1.64 (m, 2H, CCH_2CH), 1.72, 1.93 (m, 2H, two parts of ABX system, CHCH_2CH), 3.00 (m, 1H, CH_2CHCH_2), 3.23 (m, 1H, CC*H*CH=CH), 3.69 (1H, O*H*), 6.04 (1H, dd, CCHC*H*=CH, $^3J_{HH}$=3.0, =5.7 Hz), 6.38 (1H, dd, CCHCH=C*H*, $^3J_{HH}$=3.1, =5.7 Hz), 7.06 (s, 1H, C=C*H*) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$) δ=15.1, 21.0, 24.1, 26.6 ($4CH_3$), 38.3 (CH_2, CCH_2CH), 41.3 (CH, CCH_2CH), 48.1 (CH_2, $CCHCH_2$), 51.6, 54.8 (2C, $2CH_3CCH_3$), 51.6 (CH, CCHCH=CH), 90.2 (C, C=CH–*C*–O), 97.4 (C, *C*O(OH)), 132.3 (C, *C*=CH), 132.7 (CH, CCH*C*H=CH), 140.6 (CH, CCHCH=C*H*), 143.9 (CH, C=*C*H), 197.9 (C, C=C–*C*=O), 210.7 (C, *C*=O) ppm. IR (KBr) ν: 3491 (OH), 3081 and 3070 (=CH), 2986–2873 (CH, CH_2 and CH_3), 1721 (C=O), 1683 (α,β unsaturated C=O), 1633 (C=C), 1080 (C–O peroxide), 1061 (C–O, alcohol) cm^{-1}. MS (ESI, CH_2Cl_2/MeOH, positive mode, *m*/*z*): 341 $[MNa]^+$, 659 $[2MNa]^+$. HRMS (ESI, CH_2Cl_2/MeOH, positive mode, *m*/*z*): calculated for $C_{18}H_{22}O_5Na$ 341.1365, found 341.1406. Mp (Büchi)=108 °C.

5.7.2. Diastereoisomer ***11b***

R_f (pet. ether/AcOEt 8:2) 0.41. ^{1}H NMR (300 MHz, $CDCl_3$) δ=0.99, 1.32, 1.35, 1.39 (4s, 3H, $4CH_3$), 1.44, 2.30 (m, 2H, two parts of ABX system, CCH_2CH), 2.03, 2.30 (m, 2H, two parts of ABX system, CHCH_2CH), 2.78 (m, 1H, CH_2CHCH_2), 3.06 (m, 1H, CC*H*CH=CH), 6.17 (dd, 1H, CCHC*H*=CH, $^3J_{HH}$=3.0, =5.6 Hz), 6.50 (dd, 1H, CCHCH=C*H*, $^3J_{HH}$=3.2, =5.6 Hz), 6.97 (s, 1H, C=C*H*) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$) δ=15.2, 20.8, 24.5, 24.6 ($4CH_3$), 39.7 (CH_2, CCH_2CH), 42.29 (CH, CCH_2CH), 47.7 (CH_2,CCHCH_2), 51.0 (CH, CCHCH=CH), 51.7, 54.8 (2C, $2CH_3CCH_3$), 89.8 (C, C=CH–*C*–O), 97.3 (C, *C*O(OH)), 131.8 (CH, CCH*C*H=CH), 132.4 (C, *C*=CH), 142.9 (CH, CCHCH=C*H*), 143.4 (CH, C=*C*H), 198.2 (C, C=C–*C*=O); 210.8 (C, *C*=O) ppm. MS (ESI, CH_2Cl_2/MeOH, positive mode, *m*/*z*): 341 $[MNa]^+$. HRMS (ESI, MeOH, positive mode, *m*/*z*): calculated for $C_{18}H_{22}O_5Na$ 341.1365, found 341.1390.

5.8. 2,2,4,4-Tetramethyl-6-(3-(bicyclo[2.2.1]hept-5-en-2-yl))oxiranyl-cyclohexane-1,3,5-trione (12)

5.8.1. Diastereoisomer ***12a***

R_f (pet. ether/AcOEt 9:1) 0.57. ^{1}H NMR (300 MHz, $CDCl_3$) δ=0.67 and 1.66 (m, 2H, two parts of ABX system, (O)CHCHCH_2CH), 0.99 and 1.23 (m, 2H, two parts of ABX system, CHCH_2CH), 1.28, 1.34, 1.35, 1.44 (4s, 3H, $4CH_3$), 1.96 (m, 1H, (O)CHC*H*), 2.86 (m, 1H, (O)CHCHCH$_2$C*H*), 3.14 (m, 1H, (O)CHCHC*H*), 3.20 (d, 1H, C*H*(O)), 6.18 (m, 2H, C*H*=C*H*) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$) δ=19.3, 21.3, 23.9, 24.0 ($4CH_3$), 29.2 (CH_2, (O)CHCHCH_2CH), 35.8 (CH, (O)CHCH), 42.5 (CH, (O)CHCHCH$_2$CH), 45.8 (CH, (O)CHCHCH), 49.4 (CH_2, CHCH_2CH), 59.7–60.2 (2C, $2CH_3CCH_3$), 63.8 (C, O=C–*C*(O)–C=O), 73.1 (CH, C(O)*C*H), 132.6–138.0 (2CH, *C*=*C*), 201.9–202.1 (2C, 2(*C*=O)C(O)), 207.3 (C, *C*=O) ppm. MS (DCI/NH_3, CH_2Cl_2, positive mode, *m*/*z*): 320 $[MNH_4]^+$, 337 $[MN_2H_7]^+$, 622 $[2MNH_4]^+$. HRMS (DCI/CH_4, CH_2Cl_2, positive mode, *m*/*z*): calculated for $C_{18}H_{23}O_4$ 303.1596, found 303.1594.

5.8.2. Diastereoisomer ***12b***

R_f (EP/AcOEt 9:1) 0.57. ^{1}H NMR (300 MHz, $CDCl_3$) δ=0.94 and 1.88 (m, 2H, two parts of ABX system, (O)CHCHCH_2CH), 1.01 and 1.19 (m, 2H, two parts of ABX system, CHCH_2CH), 1.36, 1.40, 1.42, 1.45 (4s, 3H, $4CH_3$), 1.94 (m, 1H, (O)CHC*H*), 2.58 (m, 1H, (O)CHCH*CH*), 2.90 (m, 1H, (O)CHCHCH$_2$C*H*), 3.23 (d, 1H, C*H*(O)), 5.90 (m, 1H, CH=C*H*), 6.28 (m, 1H, C*H*=CH) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$) δ=20.5, 21.7, 23.0, 23.5 ($4CH_3$), 31.0 (CH_2, (O)CHCHCH_2CH), 36.2 (CH, (O)CHCH), 42.3 (CH, (O)CHCHCH$_2$CH), 44.6 (CH, (O)CHCHCH), 49.9 (CH_2, CHCH_2CH), 59.7, 60.2 (2C, $2CH_3CCH_3$), 63.8 (C, O=C–*C*(O)–C=O), 73.5 (CH, C(O)*C*H), 131.2 (CH, *C*=*C*), 139.2 (CH, *C*=*C*), 201.9–202.1 (2C, 2(*C*=O)C(O)), 207.3 (C, *C*=O) ppm. MS (DCI/NH_3, CH_2Cl_2, positive mode, *m*/*z*): 320 $[MNH_4]^+$, 337 $[MN_2H_7]^+$, 622 $[2MNH_4]^+$. HRMS (DCI/CH_4, CH_2Cl_2, positive mode, *m*/*z*): calculated for $C_{18}H_{23}O_4$ 303.1596, found 303.1594.

5.9. 4-((Bicyclo[2.2.1]hept-5-en-2-yl)(2-hydroxy-3,3,5,5-tetramethyl-4,6-dioxocyclohex-1-enyl)methyl)-5-hydroxy-2,2,6,6-tetramethylcyclohex-4-ene-1,3-dione (13)

R_f (pet. ether/AcOEt 8:2) 0.50. ^{1}H NMR (300 MHz, $CDCl_3$) δ=0.30 and 1.71 (m, 2H, two parts of ABX system, CHCH_2CH), 1.30 and 1.44 (m, 2H, two parts of ABX system, CHCH_2CH), 1.33, 1.35, 1.36, 1.39, 1.40, 1.42, 1.47, 1.53 (8s, 24H, $8CH_3$), 2.57 (m, 1H, CHCHC*H*CH$_2$), 2.76 (m, 1H, CH_2CHCH_2), 3.31 (m, 2H, 2C*H*CH), 5.68 (dd, 1H, CH=C*H*, $^3J_{HH}$=2.7, =5.8 Hz), 6.21 (dd, 1H, CH=C*H*, $^3J_{HH}$=3.1, =5.8 Hz), 13.36 (1H, O*H*) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$) δ=24.6, 25.1, 25.1, 25.7, 23.3, 24.5, 25.6, 36.6 ($8CH_3$), 31.7 (CH_2, CCHCHCH$_2$), 42.6 (CH, CCHCHCH$_2$C), 45.1 (CH, CCHCHCH), 49.3 (CH, CCHCHCHCH$_2$), 51.1, 51.7 (2C, $2CH_3CCH_3$), 51.8, 52.6 (2C, $2CH_3CCH_3$), 113.4–113.5 (2C, 2C(OH)=*C*), 131.3 (CH, *C*H=CH), 138.6 (CH, *C*H=CH), 189.7, 189.8 (2C, 2*C*(OH)=C), 193.3, 193.5 (2C, 2C(OH)=C–*C*=O), 212.3, 212.5 (2C, 2*C*=O) ppm. MS (DCI/NH_3, CH_2Cl_2, positive mode, *m*/*z*): 469 $[MH]^+$, 486 $[MNH_4]^+$. HRMS (DCI/CH_4, CH_2Cl_2, positive mode, *m*/*z*): calculated for $C_{28}H_{37}O_6$ 469.2590, found 469.2596.

5.10. Synthesis of endoperoxides 15a (*anti*) and 15b (*syn*)

The procedure was the same as that previously described but using 2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde (309 mg, 2.374 mmol) and syncarpic acid (433 mg, 2.374 mmol). Enone was kept under air for 6 days. After purification by silicagel column chromatography (pet. ether/AcOEt 8:2), a major fraction (252 mg) was obtained containing both endoperoxide **15a** (71 mg by estimation on ^{1}H NMR spectrum, 0.216 mmol, 9%) and ether **16** (181 mg, 0.616 mmol) besides endoperoxide **15b** (43 mg, 0.132 mmol, 6%) obtained as a white solid, epoxide **17** (22 mg, 0.071 mmol, 3%), and Michael adduct **18** (33 mg, 0.069 mmol, 3%).

5.10.1. (3R,8aS*)-3-(2,2-Dimethyl-1,3-dioxolan-4-yl)-8,8a-dihydro-8a-hydroxy-6,6,8,8-tetramethylbenzo[c][1,2]dioxine-5,7(3H,6H)-dione (**15a**)*

R_f (EP/AcOEt 7:3) 0.38. ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.08, 1.33, 1.35, 1.37 (4s, 3H, $4CH_3$), 1.48, 1.58 (2s, 3H, $2CH_3$, ketal), 4.03 and 4.14 (d, 2H, two parts of AB system, CH_2, $^2J_{HH}$=10.2 Hz), 6.91 (s, 1H, C=C*H*) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$) δ=14.8, 21.0, 24.0, 26.4 ($4CH_3$), 26.1, 26.4 ($2CH_3$, ketal), 52.0, 55.0 (2C, $2CH_3CCH_3$), 71.5 (CH_2, CCH_2O), 97.0 (C, *C*O(OH)), 103.4 (C, *C*(O)$_2$CH$_2$), 114.0 (C, *C*(O)$_2$(CH$_3$)$_2$), 132.1 (CH, C=*C*H), 135.1 (C, *C*=CH), 198.0 (C, C=C–*C*=O), 210.1 (C, *C*=O) ppm. MS: (DCI/NH_3, CH_2Cl_2, positive mode, *m*/*z*): 344 $[MNH_4]^+$. HRMS (ESI, MeOH, positive mode, *m*/*z*): calculated for $C_{16}H_{22}O_7Na$ 349.1263, found 349.1169.

5.10.2. (3R,8aR*)-3-(2,2-Dimethyl-1,3-dioxolan-4-yl)-8,8a-dihydro-8a-hydroxy-6,6,8,8-tetramethylbenzo[c][1,2]dioxine-5,7(3H,6H)-dione (**15b**)*

R_f (EP/AcOEt 7:3) 0.56. ^{1}H NMR (300 MHz, $CDCl_3$) δ=0.99, 1.29, 1.35, 1.37 (4s, 3H, $4CH_3$), 1.46, 1.54 (2s, 3H, $2CH_3$ ketal), 3.96 and 4.48 (2d, 2H, two parts of AB system, CH_2, $^2J_{HH}$=9.7 Hz), 6.96 (s, 1H, C=CH) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$) δ=14.6, 20.8, 24.0, 26.4 ($4CH_3$), 25.4, 27.3 ($2CH_3$, ketal), 51.6, 54.8 (2C, $2CH_3CCH_3$), 71.3 (CH_2, CCH_2O), 97.7 (C, *C*O(OH)), 105.3 (C, *C*(O)$_2$CH$_2$), 114.9 (C, *C*(O)$_2$(CH$_3$)$_2$), 133.7 (CH, C=*C*H), 137.5 (C, *C*=CH), 197.5 (C, C=C–*C*=O), 209.8 (C, *C*=O) ppm. MS (ESI, MeOH, positive mode, *m*/*z*): 349 $[MNa]^+$, 675 $[2MNa]^+$. HRMS (ESI, MeOH, positive mode, *m*/*z*): calculated for $C_{16}H_{22}O_7Na$ 349.1263, found 349.1169.

5.11. 2,3-Dihydro-2-(2,2-dimethyl-1,3-dioxolan-4-yl)-5,5,7,7-tetramethylbenzofuran-4,6(5*H*,7*H*)-dione (16)

R_f (EP/AcOEt 7:3) 0.38. ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.31, 1.33, 1.38, 1.41, (4s, 3H, $4CH_3$), 1.43, 1.54 (2s, 3H, $2CH_3$ ketal), 3.02 and 3.06 (2d, 2H, two parts of AB system, C=C–C*H*$_2$, $^2J_{HH}$=16.3 Hz), 4.04 and 4.36 (2d, 2H, two parts of AB system, CH_2, $^3J_{HH}$=9.6 Hz) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$) δ=24.0, 24.2, 24.7, ($4CH_3$), 25.8, 27.1 ($2CH_3$ ketal), 33.7 (CH_2, C=C–*C*H$_2$), 45.1, 55.35 (2C, $2CH_3CCH_3$), 73.6 (CH_2, CCH_2O), 108.6 (C, C=*C*–CH$_2$), 113.2 (C, *C*(O)$_2$(CH$_3$)$_2$), 116.4 (C, *C*(O)$_2$(CH$_2$)$_2$), 175.2 (C, C=*C*–O), 194.2 (C, C=C–*C*=O), 213.2 (C, *C*=O) ppm. IR (diamond compression system) ν: 2983–2876 (CH_2 and CH_3), 1717 (C=O), 1626 (C=C), 1057 (C–O) cm^{-1}. MS (DCI/NH_3, CH_2Cl_2, positive mode, *m*/*z*): $[MH]^+$ 295, $[MNH_4]^+$ 312. HRMS (DCI/CH_4, CH_2Cl_2, positive mode, *m*/*z*): calculated for $C_{16}H_{23}O_5$ 295.1545, found 295.1568.

5.12. 5-Hydroxy-4-(3-(2,2-dimethyl-1,3-dioxolan-4-yl)oxiran-2-yl)-2,2,6,6-tetramethylcyclohex-4-ene-1,3-dione (17)

R_f (EP/AcOEt 1:1) 0.49. ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.33, (s, 6H, $2CH_3$), 1.41, 1.44 (2s, 3H, $2CH_3$), 1.46, 1.54 (2s, 3H, $2CH_3$ ketal), 4.31 and 4.53 (2d, 2H, two parts of AB system, CH_2, $^2J_{HH}$=10.4 Hz), 5.15 (s, 1H, C*H*O) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$) δ=23.9, 24.0 ($4CH_3$), 25.7, 26.9 ($2CH_3$ ketal), 45.4, 55.5 (2C, $2CH_3CCH_3$), 69.4 (CH_2), 74.12 (CH), 112.6 (C, C=*C*–C=O), 113.7 (C, *C*(O)$_2$(CH_3)$_2$), 119.0 (C, *C*(O)$_2$$CH_2$), 179.5 (C, C=*C*–OH), 195.3 (C, C=C–*C*=O), 212.4 (C, *C*=O) ppm. MS (DCI/CH_4, CH_2Cl_2, positive mode, *m*/*z*): 311 $[MH]^+$. HRMS (DCI/CH_4, CH_2Cl_2, positive mode, *m*/*z*): calculated for $C_{16}H_{23}O_6$ 311.1495, found 311.1507.

5.13. 5-Hydroxy-4-((2-hydroxy-3,3,5,5-tetramethyl-4,6-dioxocyclohex-1-enyl)(2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-2,2,6,6-tetramethylcyclohex-4-ene-1,3-dione (18)

R_f (EP/AcOEt 1:1) 0.60. ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.26 (s, 6H, $2CH_3$), 1.36 (s, 12H, $4CH_3$), 3.42and 3.93 (2dd, 2H, two parts of ABX system, CH_2, $^2J_{HH}$=8.2 Hz, $^3J_{HH}$=4.6, $^3J_{HH}$=5.7 Hz), 3.99 (d, 1H, C*H*CHCH$_2$, $^3J_{HH}$=10.2 Hz), 5.17 (m, 1H, CHC*H*CH$_2$), 12.28 (1H, OH) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$) δ=24.6–27.3 ($8CH_3$), 25.5 ($2CH_3$), 37.6 (CH, *C*HCHCH$_2$), 51.6 (C, $2CH_3CCH_3$), 68.6 (CH_2, CHCH*C*H$_2$), 72.3 (CH, CH*C*HCH$_2$), 109.6 (C, *C*(O)$_2$(CH_3)$_2$), 110.9 (C, *C*=C–OH), 187.7 (C, C=*C*–OH), 195.9 (C, C=C–*C*=O), 211.8 (C, *C*=O) ppm. MS (DCI/CH_4, CH_2Cl_2, positive mode, *m*/*z*): 477 $[MH]^+$. HRMS (DCI/CH_4, CH_2Cl_2, positive mode, *m*/*z*): calculated for $C_{26}H_{37}O_8$ 477.2488, found 477.2471.

5.14. 3-Cyclobutyl-8,8a-dihydro-8a-methoxy-6,6,8,8-tetramethylbenzo[*c*][1,2]dioxine-5,7(3*H*,6*H*)-dione (19)

Endoperoxide **6** (45 mg, 0.161 mmol) was solubilized in anhydrous THF (14 mL) under argon and cooled at −78 °C. (1.3 M/hexane) butyllithium solution (170 μL, 0.221 mmol) was added dropwise. After stirring for 15 min, methyl triflate (25 μL, 0.221 mmol) was added. The mixture was kept at −78 °C for 4 h and then solution of saturated NH_4Cl was added. Aqueous phase was extracted with dichloromethane, organic phases brought together, washed with water, dried over magnesium sulfate, filtered, and evaporated. The crude mixture was purified on column chromatography of silicagel, (pet. ether/AcOEt=9:1). Endoperoxide **19** (22 mg, 0.075 mmol) is obtained in 47% yield. R_f (pet. ether/AcOEt 8:2) 0.58. ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.97, 1.27, 1.29, 1.34 (4s, 3H, $4CH_3$), 1.95 and 2.06 (2 m, 2H, two parts of ABX_2 system, $CH_2CH_2CH_2$), 2.19–2.58 (m, 4H, $2CH_2$), 3.41 (s, 3H, O*C*H$_3$), 7.61 (s, 1H, C=C*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ=13.0 (CH_2), 15.5, 21.5, 24.8, 26.0 ($4CH_3$), 30.6, 32.6 ($2CH_2$), 53.2, 54.7 (2C, $2CH_3CCH_3$), 54.4 (O*C*H$_3$), 81.2 (C, C=C–*C*O), 100.4 (C, *C*O(OCH$_3$)), 128.1 (C, *C*=CH), 142.9 (CH, C=*C*H), 199.1 (C, C=C–*C*=O), 210.5 (C, *C*=O) ppm. IR (KBr) ν: 2978–2844 (CH_2 and CH_3), 1727 (C=O), 1687 (α,β unsaturated C=O), 1631 (C=C), 1099 (C–O peroxide), 1079 (C–O) cm^{-1}. HRMS (DCI/CH_4, CH_2Cl_2, positive mode, *m*/*z*): calculated for $C_{16}H_{22}O_5$ 294.1467, found 294.1504. Mp (Büchi)=78 °C.

5.15. 3-Cyclopentyl-8,8a-dihydro-8a-methoxy-6,6,8,8-tetramethylbenzo[*c*][1,2]dioxine-5,7(3*H*,6*H*)-dione (20)

The procedure was the same as that previously described but using endoperoxide **7** (47 mg, 0.160 mmol). Methylated endoperoxide **20** (39 mg, 0.126 mmol) was obtained in 79% yield after purification by silicagel column chromatography, (pet. ether/AcOEt=9:1). R_f (pet. ether/AcOEt 8:2) 0.59. ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.00, 1.27, 1.28, 1.33, (4s, 3H, $4CH_3$), 1.60–2.40 (m, 8H, $4CH_2$), 3.44 (3H, O*C*H$_3$), 7.38 (s, 1H, C=*H*) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$) δ=15.5, 21.6, 24.7, 25.9 ($4CH_3$), 24.5, 24.9 ($2CH_2$), 35.4, 35.9 ($2CH_2$), 53.0, 54.55 (2C, $2CH_3CCH_3$), 54.48 (O*C*H$_3$), 89.6 (C, C=CH–*C*O), 100.5 (C, *C*O(OCH$_3$)), 128.4 (C, *C*=CH), 145.4 (CH, C=*C*H), 198.8 (C, CH=C–*C*=O), 210.6 (C, *C*=O) ppm. IR (diamond compression system) ν: 3060 (=CH), 2960–2833 (CH_2 and CH_3), 1726 (C=O), 1690 (α,β unsaturated C=O), 1639 (C=C), 1098 (C–O peroxide), 1050 (C–O) cm^{-1}. MS (ESI, MeOH, positive mode, *m*/*z*): 331 $[MNa]^+$, 639 $[2MNa]^+$. HRMS (ESI, MeOH, positive mode, *m*/*z*): calculated for $C_{17}H_{24}O_5Na$ 331.1521, found 331.1545. Mp (Büchi)=63 °C.

5.16. 3-Cyclohexyl-8,8a-dihydro-8a-methoxy-6,6,8,8-tetramethylbenzo[*c*][1,2]dioxine-5,7(3*H*,6*H*)-dione (21)

The procedure was the same as that previously described but using endoperoxide **9** (50 mg, 0.162 mmol). Methylated endoperoxide **21** (31 mg, 0.096 mmol) was obtained in 59% yield after purification by silicagel column chromatography, (pet. ether/AcOEt=9:1). R_f (pet. ether/AcOEt 9:1) 0.41. ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.03, 1.28, 1.30, 1.33 (4s, 3H, $4CH_3$), 1.45–1.97 (m, 10H, $5CH_2$), 3.46 (3H, O*C*H$_3$), 7.38 (s, 1H, C=*H*) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$) δ=15.6 (CH_3), 21.0, 21.05 ($2CH_2$), 21.7 (CH_3), 24.7 (CH_3), 25.0 (CH_2), 25.9 (CH_3), 31.6, 32.9 ($2CH_2$), 53.1, 54.68 (2C, $2CH_3CCH_3$), 54.76 (O*C*H$_3$), 79.7 (C, C=CH–*C*O), 100.6 (C, *C*O(OCH$_3$)), 128.5 (C, *C*=CH), 145.5 (CH, C=*C*H), 199.0 (C, CH=C–*C*=O), 210.5 (C, *C*=O) ppm. IR (KBr) ν: 3055 (=CH), 2991–2852 (CH_2 and CH_3), 1719 (C=O), 1689 (α,β unsaturated C=O), 1637 (C=C), 1105 (C–O peroxide), 1050 (C–O) cm^{-1}. MS (ESI, CH_2Cl_2/MeOH, positive mode, *m*/*z*): 345 $[MNa]^+$. HRMS (ESI, MeOH, positive mode, *m*/*z*): calculated for $C_{18}H_{26}O_5Na$ 345.1678, found 345.1711. Mp (Büchi)=56 °C.

5.17. 3-(Bicyclo[2.2.1]hept-5-en-2-yl)-8,8a-dihydro-8a-methoxy-6,6,8,8-tetramethylbenzo[*c*][1,2]dioxine-5,7(3*H*,6*H*)-dione (22)

The procedure was the same as that previously described but using endoperoxide **11a** (45 mg, 0.141 mmol). Methylated endoperoxide **22** (34 mg, 0.102 mmol) was obtained in 73% yield after purification by silicagel column chromatography, (pet. ether/AcOEt=9:1). R_f (pet. ether/AcOEt 8:2) 0.54. ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.08, 1.29, 1.31, 1.35 (4s, 3H, $4CH_3$), 1.65 (m, 2H, CH_2), 1.70 and 1.91 (2 m, 2H, two parts of ABX system, CHC*H*$_2$CH), 2.99 (m, 1H, CH_2C*H*CH$_2$), 3.17 (m, 1H, CC*H*CH=CH), 3.44 (s, 3H, O*C*H$_3$), 6.04 (1H, dd, CCHC*H*=CH, $^3J_{HH}$=3, =5.7 Hz), 6.38 (1H, dd, CCHCH=C*H*, $^3J_{HH}$=3.1, =5.7 Hz), 7.27 (s, 1H, C=C*H*) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$) δ=15.5, 21.7, 24.7, 25.9, ($4CH_3$), 37.9 (CH_2, C*C*H$_2$CH), 41.2 (CH, CCH$_2$*C*H), 48.0 (CH_2, CCH*C*H$_2$), 51.5 (CH, C*C*HCH=CH), 53.0, 54.6 (2C, $2CH_3CCH_3$), 54.6 (O*C*H$_3$), 89.5 (C, C=CH–*C*–O), 100.3 (C, *C*O(OCH$_3$)), 128.9 (C, *C*=CH), 132.7 (C, *C*=CH), 140.6 (CH, CCHCH=C*H*), 146.7 (CH, C=*C*H), 198.6 (C, C=C–*C*=O), 210.6 (C, *C*=O) ppm. IR (diamond compression system) ν: 3081 and 3061 (=CH), 2989–2869 (CH, CH_2 and CH_3), 1728 (C=O), 1688 (α,β unsaturated C=O), 1632 (C=C), 1162 (C–O), 1103 (C–O peroxide) cm^{-1}. MS (ESI, CH_2Cl_2/MeOH, positive mode, *m*/*z*): 355 $[MNa]^+$, 687 $[2MNa]^+$. HRMS (ESI, CH_2Cl_2/MeOH, positive mode, *m*/*z*): calculated for $C_{19}H_{24}O_5Na$ 355.1521, found 355.1565. Mp (Büchi)=76 °C.

5.18. Methylation of endoperoxides 15a and 15b

Methylation was performed on *anti* **15a** or *syn* **15b** (37 mg, 0.113 mmol). Methylated endoperoxides *anti* **23a** or *syn* **23b** (13 mg, 0.038 mmol) were obtained in 34% yield after purification by silicagel column chromatography (pet ether/AcOEt=9:1).

5.18.1. (3R,8aS*)-3-(2,2-Dimethyl-1,3-dioxolan-4-yl)-8,8a-dihydro-8a-methoxy-6,6,8,8-tetramethylbenzo[c][1,2]dioxine-5,7(3H,6H)-dione (**23a**)*

R_f (pet. ether/AcOEt 8:2) 0.50. ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.07, 1.29, 1.31, 1.36 (4s, 3H, $4CH_3$), 1.48, 1.58 (2s, 3H, $2CH_3$ ketal), 3.40 (3H, OCH_3), 4.03 and 4.17 (d, 2H, two parts of AB system, CH_2, $^2J_{HH}$=10.0 Hz), 7.10 (s, 1H, C=C*H*) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$) δ=15.3, 21.7, 24.8, 25.9 ($4CH_3$), 26.3, 26.4 ($2CH_3$, ketal), 53.4, 54.8 (2C, $2CH_3CCH_3$), 54.3 (OCH_3), 71.3 (CH_2, CCH_2O), 99.9 (C, $CO(OCH_3)$), 102.8 (C, $C(O)_2CH_2$), 114.0 (C, $C(O)_2(CH_3)_2$), 132.1 (CH, C=*C*H), 134.6 (C, *C*=CH), 198.9 (C, C=C–*C*=O), 209.8 (C, *C*=O) ppm. IR (diamond compression system) ν: 3065 (=CH), 2982–2876 (CH_2 and CH_3), 1727 (C=O), 1695 (α,β unsaturated C=O), 1648 (C=C), 1105 (C–O peroxide), 1088 and 1070 (C–O) cm^{-1}. MS (ESI, MeOH, positive mode, *m*/*z*): 363 $[MNa]^+$.

5.18.2. (3R,8aR*)-3-(2,2-Dimethyl-1,3-dioxolan-4-yl)-8,8a-dihydro-8a-methoxy-6,6,8,8-tetramethylbenzo[c][1,2]dioxine-5,7(3H,6H)-dione (**23b**)*

R_f (pet. ether/AcOEt 8:2) 0.62. ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.01, 1.28, 1.30, 1.34 (4s, 3H, $4CH_3$), 1.48, 1.56 (2s, 3H, $2CH_3$ ketal), 3.52 (3H, OCH_3), 3.95 and 4.41 (2d, 2H, two parts of AB system, CH_2, $^2J_{HH}$=9.6 Hz), 7.19 (s, 1H, C=C*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ=15.1, 21.6, 25.0, 25.8 ($4CH_3$), 25.6, 27.2 ($2CH_3$ ketal), 53.3, 54.7 (2C, $2CH_3CCH_3$), 54.8 (OCH_3), 71.3 (CH_2, CCH_2O), 100.8 (C, $CO(OCH_3)$), 104.7 (C, $C(O)_2CH_2$), 114.7 (C, $C(O)_2(CH_3)_2$), 140.0 (C, *C*=CH), 136.6 (CH, C=*C*H), 198.1 (C, C=C–*C*=O), 209.8 (C, *C*=O) ppm. IR (diamond compression system) ν: 3087 (=CH), 2994–2878 (CH_2 and CH_3), 1725 (C=O), 1696 (α,β unsaturated C=O), 1655 (C=C), 1105 (C–O peroxide), 1088 and 1057 (C–O) cm^{-1}. MS (ESI, MeOH, positive mode, *m*/*z*): 363 $[MNa]^+$. HRMS (ESI, MeOH, positive mode, *m*/*z*): calculated for $C_{17}H_{24}O_7Na$ 363.1420, found 363.1432.

Acknowledgements

We acknowledge the 'Ministère de l'Education Nationale' for a grant to V.B. and T. Ugolini for manuscript rereading.

Supplementary data

^{13}C NMR spectra of endoperoxides **2**, **8**, **9**, **11a**, **15a**+**16**, **15b**, **19**, **20**, **21**, **22**, **23a**, and **23b** and crystallographic data of **8**, **22**, and **23a** are presented. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.07.030.

References and notes

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12. Crystal data for **8**: $C_{16}H_{22}O_5$, *M*=294.34, monoclinic, *P*2(1)/*c*, *a*=12.4092(8) Å, *b*=11.6069(8) Å, *c*=11.0361(7) Å, α=90°, β=108.951(4)°, γ=90°, *V*=1503.40 Å^3, *Z*=4, crystal size 0.15×0.10×0.10 mm^3, 16,069 reflections (2513 independent, R_{int}=0.1489), 179 parameters, *R*1 ($I>2\sigma(I)$)=0.0550, wR_2(all data)=0.1164, largest diff. peak and hole 0.230 and −0.272 e Å^{-3} Crystal data for **22**: $C_{19}H_{24}O_5$, *M*=332.38, monoclinic, *P*2(1)/*c*, *a*=11.0364(5) Å, *b*=8.4595(4) Å, *c*=18.9412(9) Å, α=90°, β=103.9820(10)°, γ=90°, *V*=1716.00 Å^3, *Z*=4, crystal size 0.60×0.40×0.30 mm^3, 17,614 reflections (4510 independent, R_{int}=0.0262), 222 parameters, *R*1 ($I>2\sigma(I)$)=0.0406, wR_2(all data)=0.1047, largest diff. peak and hole 0.382 and −0.210 e Å^{-3} Crystal data for **23a**: $C_{17}H_{24}O_7$, *M*=340.36, triclinic, *P*−1, *a*=8.2032(7) Å, *b*=13.2769(11) Å, *c*=18.159(2) Å, α=108.917(5)°, β=98.325(5)°, γ=101.103(4)°, *V*=1789.6(3) Å^3, *Z*=4, crystal size 0.50×0.40×0.10 mm^3, 19,988 reflections (7255 independent, R_{int}=0.0368), 447 parameters, *R*1 ($I>2\sigma(I)$)=0.0495, wR_2(all data)=0.1173, largest diff. peak and hole 0.257 and −0.174 e Å^{-3} Data for **8**, **22**, and **23a** 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 **8**, **22**, and **23a**.[13] The structures were solved by direct methods (SHELXS-97),[14] and refined using the least-squares method on F^2.[15] Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-728174 (**8**), CCDC-728175 (**22**), CCDC-728176 (**23a**). 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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