Autoxidation of 2-alkylidene-1,3-cyclohexanediones as a green process to form bicyclic hemiketal endoperoxides†

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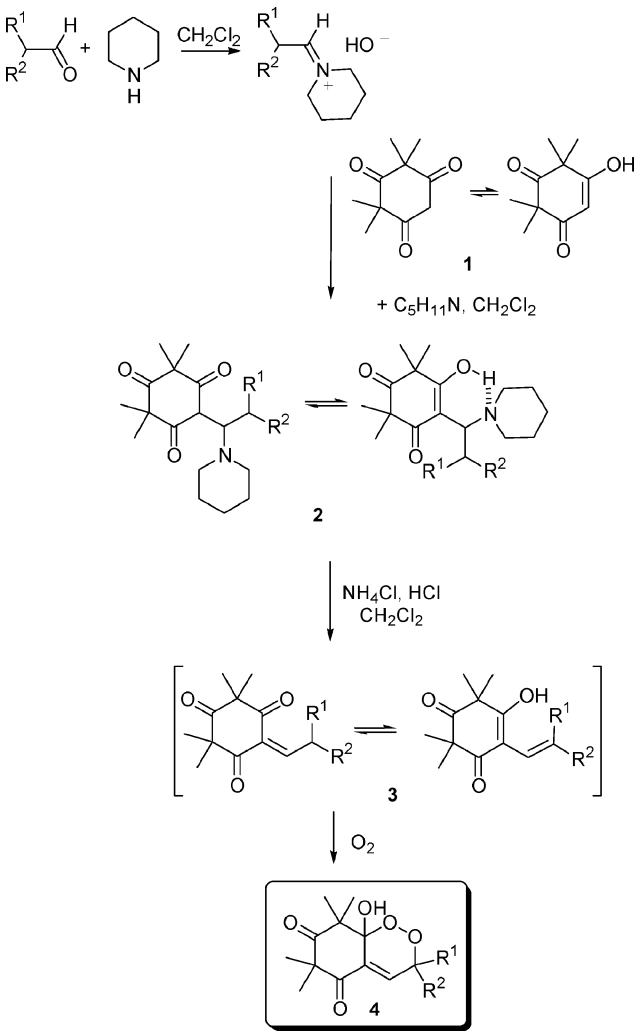
Autoxidation of 2-alkylidene-1,3-cyclohexanediones exclusively furnishes endoperoxides and could constitute an interesting green process to prepare hemiketal endoperoxides useful in medicinal chemistry. Autoxidation of 2-alkylidene-1,3-cycloheptanediones into endoperoxides is very slow while autoxidation of 2-alkylidene-1,3-cyclopentanediones leads to mixtures of oxidized products.

Since the discovery of artemisinin, a new class of endoperoxide compounds has emerged. Peroxide synthesis can be achieved with several oxygen sources such as hydrogen peroxide, ozone, singlet oxygen, and more rarely molecular oxygen.

Hydrogen peroxide addition to carbonyl compounds leads to *gem*-dihydroperoxides or to hydroperoxyhemiketals,[1] while addition to epoxides leads to β-hydroxy-hydroperoxides.[2] *gem*-Dihydroperoxides are precursors in the preparation of several cyclic peroxides such as 1,2,4,5-tetraoxanes[3] or 1,2-dioxolanes.[4] Hydroperoxy-hemiketals obtained by reaction of hydrogen peroxide with carbonyls are transformed into the more stable peroxy-hemiketals, through catalyzed etherification in acidic or basic media.[5] Following etherification, the latter are used as precursors in the synthesis of a variety of cyclic peroxides such as 1,2,4-trioxanes[6] or 1,2-dioxanes.[7] Vennerstrom *et al.*[8] used this methodology to prepare β-hydroxy-hydroperoxides which are then treated with ketones in acidic media, furnishing trioxanes.

Another way to synthesize peroxides is through the use of ozone. Ozonolysis of alkenes, or more generally enol ethers and oxime ethers, is the main route to the peroxycarbenium ion species which is the reactive intermediate in peroxide formation.[1] In this way, O'Neill *et al.* synthesized yingzhaosu A.[9] Dussault and Dai[10] described the synthesis of plakinic acid A analogs. Nojima *et al.*[11] have used electrophilic cyclisation of unsaturated hydroperoxyketals, obtained from peroxycarbenium ion quenching by unsaturated alcohols, to form 1,2,4-trioxanes. Vennerstrom and Dong[12] showed that ozonolysis of *O*-methyl oximes is an alternative way to prepare dispiro-tetraoxanes. Ozone treatment of oximes and ketones leads to 1,2,4-trioxolanes, which were revealed to be good antimalarial candidates.[13]

Singlet oxygen is also used as an interesting source of oxygen to access peroxide derivatives *via* the Schenck reaction, [4 + 2] or [2 + 2] cycloadditions. Hofheinz *et al.*[14] described the synthesis of arteflene using the Schenck reaction. Singh[15] and Bloodworth and Shah[16] independently synthesized trioxanes by photooxygenation of allylic alcohols or olefins followed by acid-catalyzed condensation of carbonyl compounds on hydroperoxides. Singlet oxygen [4 + 2] cycloaddition on cyclopentadiene was developed by Jefford *et al.*[17] during fenozan (BO7) synthesis. This methodology has been reinvestigated by Meunier *et al.* in the synthesis of trioxaquines.[18] Jefford *et al.*[19] have also shown that singlet oxygen reacts through a [2 + 2] cycloaddition on enol ethers furnishing 1,2-dioxetanes, which,



Scheme 1 General access to G-factor analogs.

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at low temperature and with acid catalysis react with ketones leading to the desired 1,2,4-trioxanes. Posner *et al.*[20] modified this method, using thio enol ethers instead of enol ethers.

Molecular oxygen has scarcely been used as its reactivity is low. Interestingly however, it could be used in the preparation of 3-hydroxy-1,2-dioxanes. O'Neill *et al.*[21] optimized a route to spirotrioxanes *via* the Co(II) catalyzed preparation of triethylsilyl peroxides. Posner and Bachi *et al.*[22] perfected in 1998 a radical process called TOCO (thiol-olefin co-oxygenation) giving access to dioxanes or trioxanes *via* formation of a peroxyl radical intermediate. O'Neill *et al.* reinvestigated this process[23] to describe a 1,2,4-trioxane synthesis. Posner *et al.*[24] synthesized cyclic peroxyketals using a Snider and Shi protocol,[25] photoenolisation followed by oxygenation. Baumstark *et al.*[26] described the synthesis of pentasubstituted 3-hydroxy-1,2-dioxolanes *via* O_2 trapping of intermediates generated during the thermolysis of cyclic α-azo hydroperoxides.

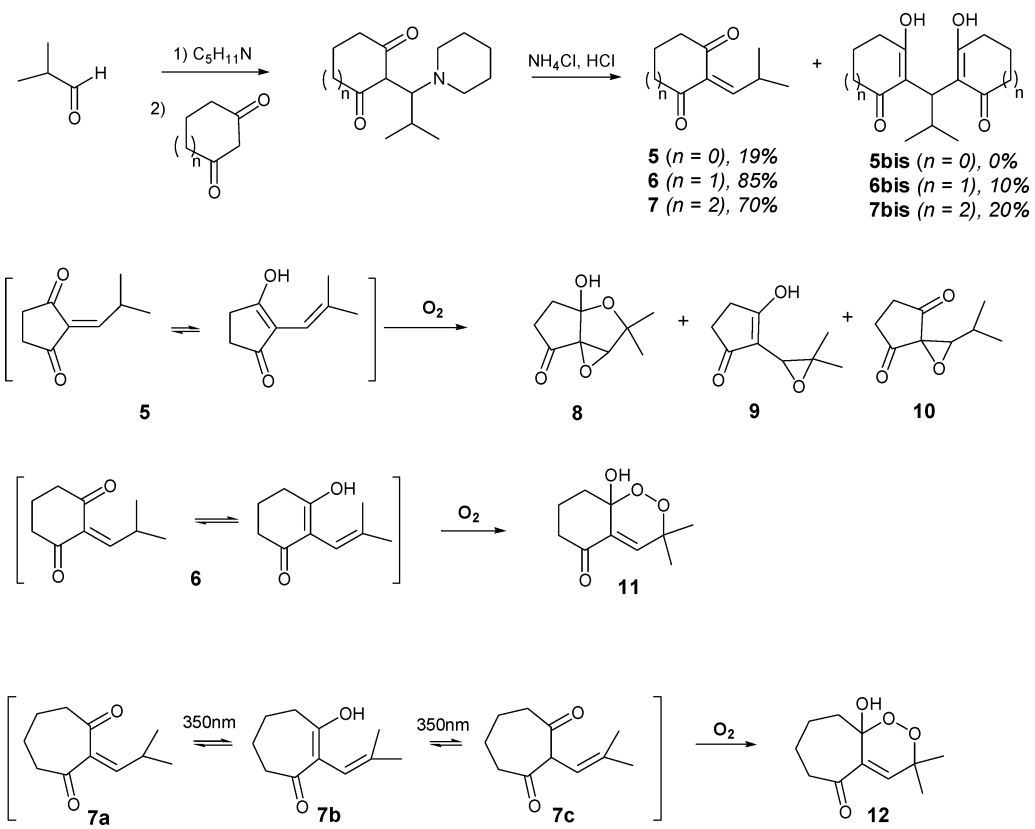
We wish to describe here a "green process" giving 3-hydroxy-1,2-dioxanes directly. In fact, we have been confronted by an intriguing spontaneous oxygen uptake by precursors of G-factors, natural compounds extracted from *Eucalyptus grandis* leaves.[27,28] This reaction works whatever the solvent (except hydroxylated ones), even without solvent and works well on large scale. This observation allows us to use this autoxidation as the key step in the synthesis of antimalarial endoperoxides belonging to the G-factor family.[29] We found that this reaction could proceed *via* addition of $^3O_2$ to dienol compounds, thereby yielding triplet biradical intermediates characterized by EPR studies, after trapping to furnish long-lived radicals.[30]

This methodology has been used previously, in the course of antimalarial endoperoxide synthesis. Thus, the parent compounds were obtained through a modified Knoevenagel type two-step procedure *i.e.* Mannich reaction between syncarpic acid (**1**) and the corresponding aldehydes, followed by acidic treatment of the Mannich base (**2**). Subsequent spontaneous time-modulated oxygen uptake by the precursors **3** exclusively led to the expected endoperoxides **4** (Scheme 1).[31]

Schobert *et al.*[32] have also previously reported that 3-alkylidenedihydrofuran-2,4-diones are slowly autoxidized in air to the corresponding hemiketal endoperoxide lactones.

Widening of this autoxidation process could permit the development of an environmentally friendly alternative to produce endoperoxides for the antimalarial fight, leading to a new class of drugs. We want to describe in this work the autoxidation of precursors coming from various 1,3-cycloalkanediones and evaluate the limits of the reaction: size of the 1,3-dione ring, nature of the involved aldehyde.

In each series (n = 0, 1, 2) Mannich bases were prepared by addition of the corresponding iminium species, formed by reaction of one equivalent piperidine with the aldehyde, to 1,3-cyclopentane-, hexane- or heptanedione in dichloromethane solution. Slow addition of iminium to diketone was necessary in these series to minimize formation of Michael adducts. Mannich bases so obtained were then treated with acidic media and 2-alkylidene-1,3-cycloalkanediones were obtained in equilibrium with the dienol forms. Yields of 2-alkylidene-1,3-cycloalkanedione precursors were estimated on the basis of ^{1}H NMR spectra of the crude mixtures. Next,



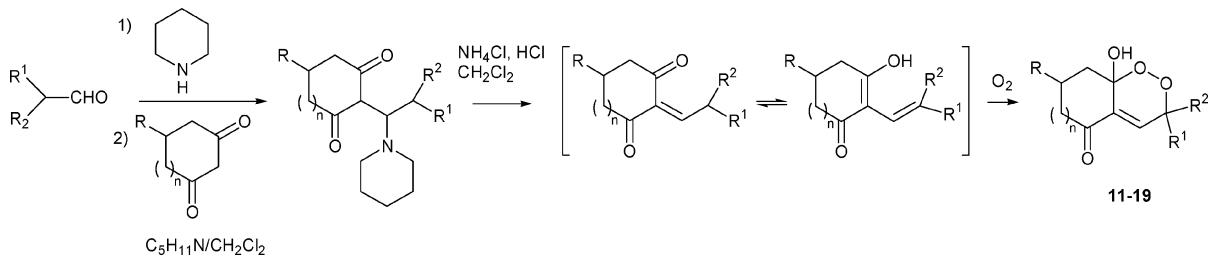
Scheme 2 Autoxidation of 2-alkylidene-1,3-cycloalkanediones.

precursors were submitted to oxygen uptake. Autoxidation was followed by ^{1}H NMR spectroscopy and crude mixtures purified by silica gel column chromatography.

2-Alkylidene-1,3-cyclopentadione **5** was obtained in low yield (19%) after acidic treatment of the corresponding Mannich base. Oxygen uptake also took place with this structure but surprisingly, the endoperoxide was not obtained. Autoxidation led to three new compounds which were isolated by silica gel chromatography and their structures were elucidated by 2D NMR and mass spectroscopy. Epoxides **8**, **9**, **10** were characterized respectively in 25%, 8% and 26% yields from precursor **5**. Epoxides **9** and **10** probably resulted from the oxidation of the corresponding dienol or enone by an intermediate hydroperoxide. A polar fraction could not be isolated and identified (Scheme 2).

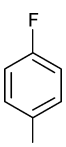
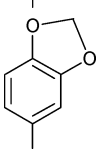
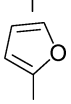
In the case of 2-alkylidene-1,3-cyclohexanedione, endoperoxide **11** was obtained as the sole product from autoxidation in an overall yield of 72% after three steps starting from 1,3-cyclohexanedione, with 10% of Michael bis-adduct, after 36 h.

Preparation of 2-alkylidene-1,3-cycloheptanedione **7** was achieved with 70% yield according to ^{1}H NMR analysis and 20% of bis-adduct **7bis** was also obtained, probably a result of the instability of the corresponding Mannich base. Autoxidation by air was then quite slow in this case. After 20 days, a mixture of oxidized products was separated by column chromatography on silica gel: endoperoxide **12** was obtained in 13% yield, accompanied by degradation products. We have previously observed,[33] that the determining step is probably enolization. So, photoenolization in dichloromethane under argon was then carried out on enone **7a** using a Rayonet apparatus equipped with 350 nm low-pressure mercury lamps. Enolization was followed by ^{1}H NMR spectroscopy. After irradiation for 30 min, 10% of the enone form **7a** remained along with two other products: dienol **7b** (54%) and deconjugated



Scheme 3 Preparation of bicyclic hemiketal endoperoxides.

Table 1 Overall yield and autoxidation time for the preparation of the bicyclic endoperoxides **11–19**

Product	*n*	R	R^1 R^2	Overall yield (3 steps) (%)	Autoxidation time/days
11	1	H	H_3C CH_3	72	1.5
13	1	Ph	H_3C CH_3	53	1
14	1	Ph		66	2
15	1	Ph		72	2
16	1		H_3C CH_3	64	6
17	1		H_3C CH_3	54	2
18	1		H_3C CH_3	22	2
12	2	H	H_3C CH_3	40	5[a]
19	2	H		23	30

[a] After enone irradiation at 350 nm for 30 min.

enone **7c** (34%). Afterwards the solution was kept under an air atmosphere and aliquots were analyzed by ^{1}H NMR spectroscopy. Autoxidation was faster since precursors **7** disappeared after five days. Endoperoxide **12** was formed in 40% yield (Scheme 2).

We then decided to extend this reaction to commercial 1,3-cyclohexanediones and to vary the aldehydes. The same protocol as previously described was used to obtain the precursors which were then submitted to oxygen uptake (Scheme 3). Results are given in Table 1. Yields of endoperoxides were calculated over the three steps, from the starting 1,3-cycloalkanedione. In the case of 5-(2-furyl)cyclohexenedione, the yield of endoperoxide **18** was low. It seems that the precursor deteriorated to a polar fraction. Also, endoperoxide was obtained after column chromatography on silica gel but could not be identified. Except **18**, yields of endoperoxide (**11–17**) from 1,3-cyclohexanedione are moderate to good. The kinetics of oxygen uptake depend on both the nature of the cycloalkanedione and that of the starting aldehyde. Formation of endoperoxide **16** took six days while one or two days were sufficient to form **11**, **13** and **17**. The precursor obtained from cyclohexanecarboxaldehyde and cycloheptadione took up oxygen very slowly (30 days) to furnish endoperoxide and **19**. The yield of 23% for the formation of **19** can be explained after analysis of 1H NMR spectra: firstly the Michael bis-adduct is formed in 38% yield during the preparation of the precursor, and then the precursor itself deteriorates as autoxidation took more than thirty days. But endoperoxide **19** is the only autoxidation product isolated.

This work allowed us to fix the limits of the autoxidation reaction. One of the limits is the size of the 2-alkylidene-1,3-cycloalkanediones: it works well and gives good yields of endoperoxides starting from 1,3-cyclohexanediones. Autoxidation is very slow in the case of 2-alkylidene-1,3-cycloheptanediones, and does not furnish endoperoxides in the case of 2-alkylidene-1,3-cyclopentanediones. Nevertheless this autoxidation reaction could be a good alternative to prepare bicyclic hemiketal endoperoxides in one step from 2-alkylidene-1,3-cyclohexanediones and this under mild conditions. In addition, it fulfils the principles of green chemistry: the reaction works at room temperature, at ambient pressure, prevents waste, maximizes atom economy and works whatever the solvent and even without solvent.

Experimental section

General procedure for the preparation of endoperoxides

To aldehyde (1 eq.) solubilised in anhydrous dichloromethane is added piperidine (1 eq.) at room temperature, under argon. Cycloalkanedione (1 eq.) is solubilised in anhydrous dichloromethane and piperidine (1 eq.) is added. After 25 min, the dione solution is slowly poured onto the iminium solution. The mixture is shaken for thirty minutes then concentrated. The Mannich base is obtained as a solid. The mixture is then dissolved in dichloromethane, treated with saturated NH_4Cl in 1 M HCl solution. After 30 min, the organic phase is washed with water then dried on magnesium sulfate, filtered and evaporated. The enone is solubilised in dichloromethane and left under air. Then the raw mixture is concentrated and purified by silica gel column chromatography (petroleum ether–ethyl acetate). Endoperoxides are obtained as white solids. Experimental and spectral data of all new compounds are given in the ESI.†

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