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Biobased aldehydes from fatty epoxides through thermal cleavage of β-hydroxy hydroperoxides

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Abstract: The ring-opening of epoxidized methyl oleate by aqueous H_2O_2 has been studied using tungsten and molybdenum catalysts to form the corresponding fatty β-hydroxy hydroperoxides. It was found that tungstic acid and phosphostungstic acid gave the highest selectivities (92-93%) towards the formation of the desired products, thus limiting the formation of the corresponding fatty 1,2-diols. The optimized conditions were applied to a range of fatty epoxides to give the corresponding fatty β-hydroxy hydroperoxides with 30-80% isolated yields (8 examples). These species were fully characterized by ^{1}H and ^{13}C NMR, HPLC-HRMS and their stability was studied by DSC. The thermal cleavage of the β-hydroxy hydroperoxide derived from methyl oleate was studied both in batch and flow conditions. It was found that the thermal cleavage in flow conditions gave the highest selectivity towards the formation of aldehydes with limited amounts of byproducts. The aldehydes were both formed with 68% GC yield and nonanal and methyl 9-oxononanoate were isolated with 57 and 55% yield, respectively. Advantageously, the overall process does not require large excess of H_2O_2 and only generates water as a byproduct.

Introduction

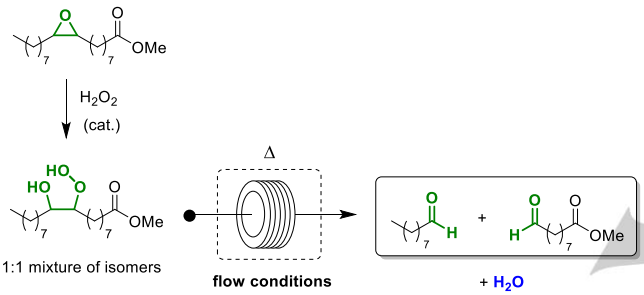
Aldehydes are ubiquitous in organic chemistry as they serve as platform towards other organic functions such as alcohols, carboxylic acids, acetals, imines, amines, and many others.[1] For several years now, the production of bio-based building-blocks from biomass as a renewable feedstock has become the subject of very intense research.[2] Contrary to carboxylic acids, only a few bio-based aldehydes are readily accessible from renewable resources. On the one hand, furanic aldehydes such as furfural,[3] 5-hydroxymethyl furfural (5-HMF)[4] and 2,5-diformylfuran[5] can be obtained from lignocellulosic biomass. In addition, other aromatic aldehydes such as vanillin and its derivatives can be produced from lignin.[6] On the other hand, vegetable oils are interesting renewable resources[7] to prepare aliphatic aldehydes.[8]

Hydroformylation of unsaturated vegetable oils and their fatty acid derivatives can give access to the corresponding homologated branched aldehydes.[9] However, despite its high atom-economy and feasibility at the industrial scale, hydroformylation involves the use carbon monoxide and hydrogen, thus requiring specialized high-pressure equipments. Complementarily, the cleavage of unsaturated fatty acid derivatives can produce aliphatic linear aldehydes. These aldehydes are of prime importance since they can used to prepare 100% bio-based surfactants by reductive etherification of polyols and sugar derivatives.[10] In addition, functionalized aldehydes can be transformed to monomers for the preparation of polyesters and polyamides through reduction or reductive amination, respectively.[11] The cleavage of fatty acid derivatives is usually carried out in the presence of strong oxidants (*i.e.*, oxidative cleavage).[12] This means that fatty aldehydes are difficult to obtain selectively through these methods since they are readily oxidized to carboxylic acids under these conditions. In this context, other strategies should be employed.

The cleavage of fatty epoxides or 1,2-diols to aldehydes was traditionally be carried out using HIO_4 or $NaIO_4$, respectively.[13] However, the use of these stoichiometric oxidants leads to the generation of large quantities of waste that could not be valorized. One of the most efficient, clean and general method to produce fatty aldehydes is reductive ozonolysis.[14] In that case, unsaturated fatty acids are over-oxidized with ozone to give the corresponding ozonides. These reactive intermediates are then reduced - typically using zinc, dimethylsulfide, triphenylphosphine or hydrogen - to aldehydes, thus limiting the formation of carboxylic acids as contaminants. Reductive ozonolysis is very attractive from an atom-economy point of view but suffers from the use of ozone that is extremely toxic for both humans and environment. Moreover, ozonolysis is a very energy-intensive process as ozone is produced from oxygen using an electric discharge. Recently, our group has reported an alternative approach consisting in the catalytic cleavage of fatty α-hydroxyketones to aldehydes under non– oxidative conditions. First, α-hydroxyketones were prepared by selective catalytic oxidation or dehydrogenation of fatty 1,2-diols.[15] Then, these intermediates were organocatalytically cleaved by retro-benzoin condensation in the presence of thiazoliums salts to give the corresponding aldehydes.[16] Albeit that this catalytic route could be attractive, it has not been demonstrated on a large scale yet. Finally, it was shown that ricinoleic derivatives, obtained from castor oil, can be thermally cleaved at high temperature (typically >300°C) to give bio-based heptanal and undecylenic acid through a retro-ene reaction.[17] Noteworthy, this process is carried out on the industrial scale since undecylenic acid can be further converted to 11-aminoundecanoic acid, which is the precursor of nylon-11 (Rilsan®). Despite that this cleavage

process is specific to ricinoleic derivatives and could not been applied to other fatty acid derivatives, it clearly demonstrates that the thermal cleavage of vegetable oil derivatives can be an economically-viable route. However, so far, the thermal cleavage of other fatty acid derivatives has been largely underexploited. Recently, the cleavage of fatty epoxides to aldehydes has been proposed using H_2O_2 as an oxidant in the presence of WO_3,[18] WO_3/MCM-41,[19] and H_2WO_4@Al-MCM-41,[20] even at room temperature. However, in these studies, the authors have only reported GC yields and no aldehydes were isolated.[21] In sharp contrast, in the present work, we demonstrate that these reported conditions do not lead to the formation of aldehydes but only produce β-hydroxy hydroperoxide species as reaction intermediates (*vide infra*).

In this context, we now report here the preparation, the isolation and the characterisation (including DSC) of fatty β-hydroxy hydroperoxides prepared from epoxides. Moreover, we also report their thermal cleavage into fatty aldehydes in batch and in flow (Scheme 1).[22]



Scheme 1. Cleavage of fatty epoxides to aldehydes through β-hydroxy hydoperoxides.

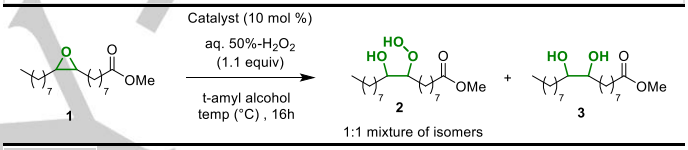
Results and Discussion

Preparation of fatty β-hydroxy hydroperoxides

The chemistry of β-hydroxy hydroperoxides is relatively unexplored.[23] These species are usually prepared by ring-opening of epoxides with H_2O_2.[24] Early works used Brönsted acids as catalysts such as $HClO_4$[25] and CF_3CO_2H.[26] Moreover, Lewis acids such as $SnCl_4$,[27] $SbCl_3/SiO_2$[28] and phosphomolybdic acid[29] (PMA) were also used to promote the reaction. Recently, magnetic nanoparticules-supported phosphomolybdate[30] and nano-graphene oxide-supported molybdenum[31] were reported as recoverable and recyclable catalysts. Despite that these methods provide β-hydroxy hydroperoxides with high yields, they require the use of neat or ethereal H_2O_2. In sharp contrast with other oxidized fatty derivatives, fatty β-hydroxy hydroperoxides has been scarcely reported. To the best of our knowledge, the first synthesis of an oleochemical β-hydroxy hydroperoxide was reported by Hiroko *et al.* in a patent.[32] In this work, methyl oleate was treated with 5 equivalents of aqueous 30% H_2O_2 at 35°C, in the presence of tungstic acid. Under these conditions, the corresponding β-hydroxy hydroperoxides was obtained with only 28% yield. Similarly, Ruffo *et al*. have reported the direct oxidation of oleic acid using an excess of 30% H_2O_2 (4 equiv.) in the presence of tungstic acid.[33] After 4 hours at 70°C, the desired β-hydroxy hydroperoxide was obtained with only 45%, mainly due to the formation (45% NMR yield) of the corresponding 1,2-diol as a by-product. Overall, these two works show that the direct oxidation of oleic acid derivatives is giving fatty β-hydroxy hydroperoxides with low yields. This is probably due to the use of a large excess of H_2O_2, resulting in the production of many by-products.

In this context, we have first investigated the preparation of fatty β-hydroxy hydroperoxides by ring-opening of epoxidized methyl oleate using a 35% aqueous solution of H_2O_2. Several parameters were screened such as the nature of the catalyst, the catalyst loading, the concentration of starting material and the temperature. However, despite a full conversion of the starting material, the selectivity did not reach more than 80% due to the formation of the corresponding 1,2-diol. This diol is formed by ring-opening of the epoxide with water, that is a competing nucleophile for hydrogen peroxide. Therefore, in order to limit the formation of this diol, a 50% aqueous solution of H_2O_2 was used for further optimization.[34] A range of catalysts was first screened for the ring-opening of epoxidized methyl oleate **1** using aq. 50% H_2O_2 (Table 1).

Table 1. Optimization for the preparation of fatty β-hydroxy hydroperoxides by ring-opening of epoxidized methyl oleate with H_2O_2.[a]



Entry	Cat. (loading, mol%)	Temp. (°C)	Conv.[b] **1** (%)	Ratio[b] **2** (%)	Ratio[b] **3** (%)
1	MoO_4 (10)	20	16	11	5
2	WO_3 (10)	20	6	6	0
3	PMA (10)	20	> 99	85	15
4	H_2WO_4 (10)	20	> 99	93	7
5	PTA (10)	20	> 99	20	66
6	PTA (1)	20	> 99	80	20
7	PTA (0.1)	20	> 99	90	10
8	PTA (0.1)	10	> 99	92	8
9	PTA (0.1)	5	67	61	6
10	PTA (0.1)	0	50	44	6
11	-	10	6	3	3

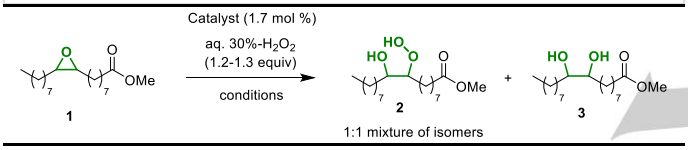
[a] Reaction conditions: epoxide **1** (1.00 g, 2.90 mmol), aq. 50%-H_2O_2 (0.22 mL, 3.18 mmol, 1.1 equiv), catalyst (0.1-10 mol%), *tert*-amyl alcohol (12 mL), 20°C, 16 hours. [b] Conversion and ratio were determined by HPLC. PMA: phosphomolybdic acid ($H_3PO_4.12MoO_3$), PTA: phosphotungstic acid ($H_3PO_4.12WO_3$).

The reaction was performed in *tert*-amyl alcohol at 20°C for 16 hours. Molybdenum and tungsten oxides were first tested but they gave poor results (Table 1, entries 1-2). The use of phosphosmolybdic acid (PMA) allows to reach full conversion and the desired peroxide **2** was obtained with 85% selectivity (Table 1, entry 3). A slightly better selectivity (93%) was

obtained with tungstic acid (Table 1, entry 4). Surprisingly, phosphotungstic acid (PTA) only give 20% of **2** and the corresponding 1,2-diol was obtained as the major product with 66% HPLC ratio (Table 1, entry 5). However, by decreasing the catalyst loading from 10 to 0.1 mol%, the selectivity towards **2** can be improved until 90% (Table 1, entries 6-7). Moreover, a selectivity of 92% can be reached by decreasing the temperature to 10°C (Table 1, entry 8). However, no further improvement can be achieved by decreasing the temperature to 5 or 0°C (Table 1, entries 9-10). Finally, a blank experiment was carried out without catalyst under the optimized conditions. Under these conditions, the conversion of **1** reached 6% and only 3% of peroxide **2** was formed (Table 1, entry 11). This result demonstrates the crucial role of PTA to activate H_2O_2, as recently reported in a patent.[35]

From our results, it is striking to see that only β-hydroxy hydroperoxides were produced and no aldehydes were obtained, in sharp contrast with reported studies carried out under similar conditions.[18-20] In order to understand these differences, we have reproduced the conditions previously described in the literature with unsupported WO_3 and H_2WO_4 (Table 2). The data presented below is the average of triplicates (see ESI).

Table 2. Reproduction of previously reported conditions.



Entry	Cat. (loading, mol%)	Temp. (°C)	Conv.[d] **1** (%)	Ratio[d] **2** (%)	Ratio[d] **3** (%)
1[a]	WO_3 (1.7)	70	5	4	1
2[b]	WO_3 (1.7)	25	74	58	16
3[c]	H_2WO_4 (1.7)	25	> 99	85	15

[a] Conditions taken from ref. 18: epoxide **1** (1.56 g, 5 mmol), aq. 30%-H_2O_2 (6.5 mmol, 1.3 equiv), WO_3 (0.085 mmol, 1.7 mol%), neat, 70°C, 20 min [b] Conditions taken from ref. 20: epoxide **1** (3.12 g, 10 mmol), aq. 30%-H_2O_2 (12 mmol, 1.2 equiv), WO_3 (0.17 mmol, 1.7 mol%), tert-butanol (5 mL), 25°C, 18h [c] Conditions taken from ref. 20: epoxide **1** (3.12 g, 10 mmol), aq. 30%-H_2O_2 (12 mmol, 1.2 equiv), H_2WO_4 (0.17 mmol, 1.7 mol%), tert-butanol (5 mL), 25°C, 2h. [d] Conversion and ratio were determined by HPLC.

Using WO_3 at 70°C for 20 min under neat conditions,[18] the conversion of **1** was only 5% and β-hydroxy hydroperoxide **2** was obtained with 4% HPLC ratio (Table 2, entry 1). Using either WO_3 or H_2WO_4 at room temperature (25°C) in tert-butanol[20] led to 74 and 99% conversion and the HPLC ratio of β-hydroxy hydroperoxide **2** reached 58 and 85%, respectively (Table 2, entries 2-3). Our results clearly demonstrate that the reported conditions are adequate to form β-hydroxy hydroperoxides but are ineffective for producing aldehydes, contrary to what was previously claimed.[18-20] This is explained by the fact that, in these works, the yield of aldehydes was determined by GC without checking the full conversion of β–hydroxy hydroperoxide intermediates (*e.g.*, by NMR or HPLC). Therefore, it is misguiding because we found that β–hydroxy hydroperoxides readily decomposed in the GC injector to form the desired aldehydes during the analysis (vide infra).

Then, the scope for the ring-opening of epoxides with H_2O_2 was next investigated with a range of fatty epoxides under our optimized conditions (Figure 1).

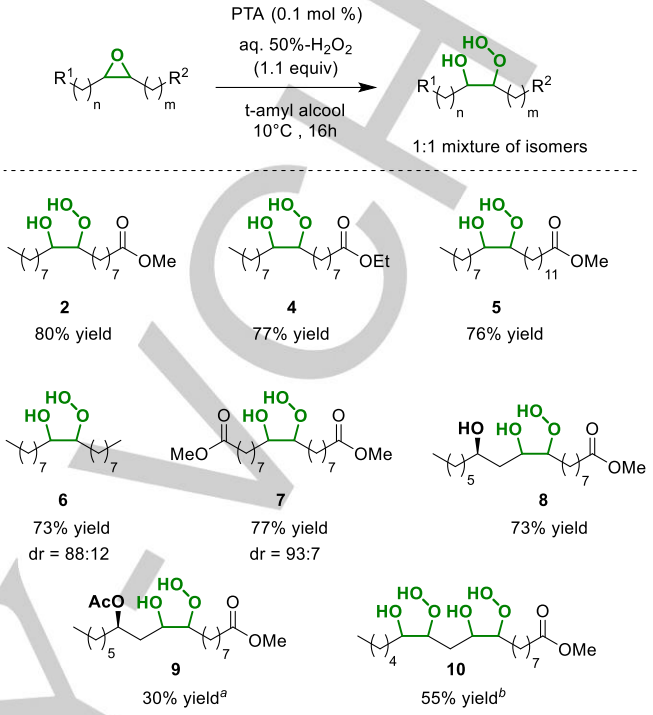


Figure 1. Scope for the formation of fatty β-hydroxy hydroperoxides. [a] The corresponding 1,2-diol was recovered as the main product. [b] 0.2 mol% of PTA was used (0.1 mol% by epoxide function) and 2.2 equiv of 50%-H_2O_2.

Epoxidized methyl oleate **1** gave the corresponding β-hydroxy hydroperoxide **2** with 80% isolated yield after purification by column chromatography. This demonstrates that fatty β-hydroxy hydroperoxides are quite robust species and are not sensitive to slightly acidic conditions such as silica. Compound **2** was first characterized by NMR. In the ^{1}H NMR spectrum, the chemical shifts at 11.2 and 4.3 ppm are characteristic signals for -OOH and -OH groups, respectively (Figure 2).

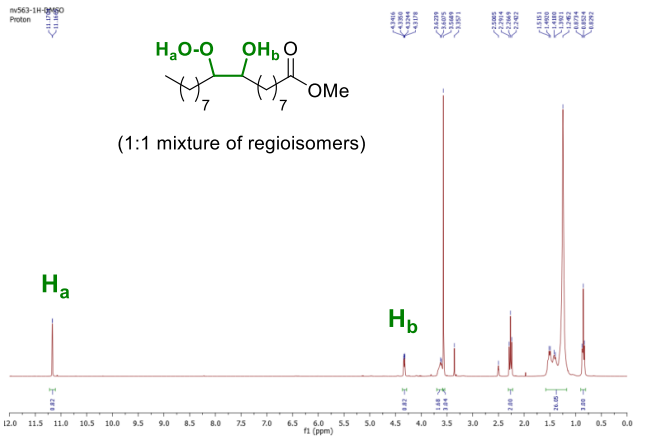


Figure 2. ^{1}H-NMR spectrum (300 MHz, DMSO-d_6) of β-hydroxy hydroperoxide **2**.

Moreover, two signals at 69 and 87 ppm in ^{13}C NMR clearly indicate the presence of the two CH of the β-hydroxy hydroperoxide function (see spectrum in ESI). Finally, the mass of **2** was also confirmed by HPLC-HRMS (see ESI). Then, ethyl oleate was also considered and it gave the corresponding β-hydroxy hydroperoxides **4** with 77% isolated yield. Similarly, hydroperoxide **5**, obtained from epoxidized methyl erucate, was obtained with 76% isolated yield. It should be noted that products **2**, **4**-**5** were obtained as a 50:50 mixture of regioisomers. The fatty epoxides derived from the self-metathesis products of methyl oleate were also used as starting materials and the corresponding β-hydroxy hydroperoxides **6** and **7** were isolated with 73% and 77% yield, respectively. For methyl ricinolate derivatives, very contrasting results were obtained: hydroperoxide **8** was obtained with 73% yield starting from epoxidized methyl ricinoleate (*i.e.* with unprotected alcohol at the position 12), while its *O*-acyl-protected analogue only gave hydroperoxide **9** with 30% yield. In that case, the corresponding 1,2-diol was formed as the major compound. The presence of the 12-OAc group may bring enough steric hindrance to prevent the addition of H_2O_2 and thus favours the nucleophilic addition of water. Finally, the bis-epoxide prepared from methyl linoleate was also subjected to the ring-opening with H_2O_2 and the corresponding bis-(β-hydroxy hydroperoxide) **10** was isolated with 55% yield. Interestingly, the product is a mixture of 8 isomers (as observed by ^1H NMR) resulting from unselective nucleophilic addition of H_2O_2 to a mixture of *cis-cis* and *cis-trans* epoxides. However, this lack of selectivity is not a problem considering that all isomers will be thermally cleaved to give the corresponding aldehydes.

Thermal cleavage of fatty β-hydroxy hydroperoxides

The cleavage of β-hydroxy hydroperoxides has been scarcely reported in the literature. Early works showed that these species can undergo acid-[36] or base-catalyzed[37] decomposition to give a variety of carbonyl compounds. More recently, Salomon *et al.* have investigated the fragmentation of hydroperoxide species in water under physiological conditions.[38] The authors have shown that the combination of vitamin C and metal cations such as Fe^{3+} and Cu^{2+} can give aldehydes – as hydrated form – with up to 66% yield. While studying the oxidative cleavage of olefins to carboxylic acids, Venturello *et al.* have also shown that an aliphatic β-hydroxy hydroperoxide can decompose at 85°C in the presence of a quaternary ammonium dioxoperotungstate.[39] In that case, the conversion reached 63% and the selectivity towards aldehydes was only 62% due to the formation of the corresponding acids (11%), α-hydroxyketone (14%) and 1,2-diol (8%) as byproducts. During the characterization of β-hydroxy hydroperoxide **2** by gas chromatography, we observed that the compound was not detected on the GC chromatogram, suggesting that it was completely degraded.[22] However, the chromatogram was clean with 2 major peaks, that were assigned to nonanal **11** and methyl 9-oxononanoate (methyl azelaaldehydate) **12** (Figure 3). A minor product was also detected and was assigned to the corresponding α-hydroxyketone **13**. This demonstrates that hydroperoxide **2** was totally converted in the GC injector (set at 300°C) to give the corresponding aldehydes. Hence, we envisioned that β-hydroxy hydroperoxide **2** could be selectively cleaved to the corresponding aldehydes by thermal cleavage under catalyst-free conditions.

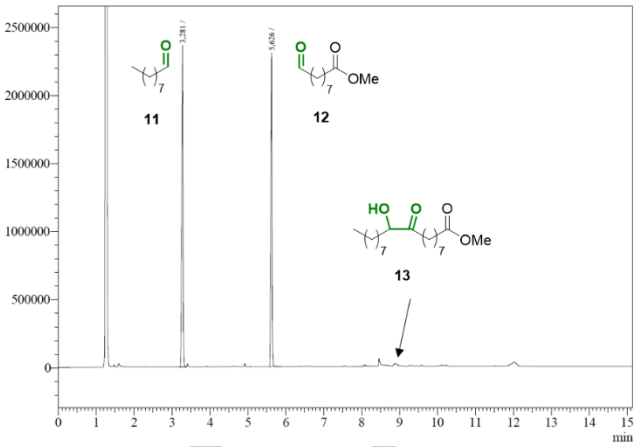


Figure 3. GC Chromatogram of β-hydroxy hydroperoxide **2** showing its decomposition to aldehydes (injector temperature = 300°C).

However, hydroperoxides species are known to be energetic compounds that could present safety risks. That is the reason why the thermal stability of fatty β-hydroxy hydroperoxide **2** (neat) was first studied by Differential Scanning Calorimetry (Table 3 and ESI).

Table 3. Comparison of decomposition enthalpies of fatty β-hydroxy hydroperoxides and ozonides.[a]

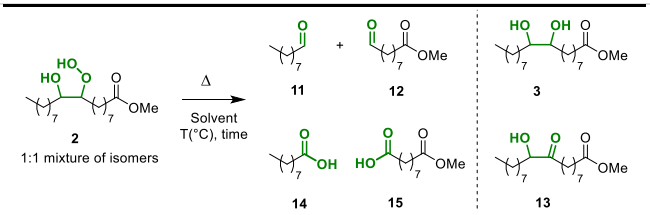
Entry	Fatty compound	MW (g/mol)	DSC decomposition enthalpy		T (°C)
			(J/g)	(KJ/mol)	
1	Hydroperoxide **2**	346.5	- 611	- 211	107
2	Hydroperoxide **4**	360.5	- 628	- 226	113
3[40]	Ethyl oleate ozonide	358.5	- 684	- 245	156
4[41]	Ethyl oleate ozonide	358.5	- 742	- 266	137
5[41]	Ethyl elaidate ozonide	358.5	- 737	- 264	139

[a] Values obtained from the thermal analysis by DSC.

The thermal analysis shows that compound **2** decomposes with a peak at 107°C and the decomposition enthalpy reaches -611 J/g (Table 3, entry 1). Similar results were obtained with the β-hydroxy hydroperoxide derived from ethyl oleate (Table 3, entry 2). The thermal analysis data for the other fatty β-hydroxy hydroperoxides is given in the supporting information. By comparison, the DSC analysis of the thermal decomposition of the ozonides prepared from ethyl oleate gives a decomposition enthalpy of -684 J/g and a decomposition temperature of 156°C, as reported by Cataldo (Table 3, entry 3).[40] In another studies, the same author has also shown that the ozonides prepared from either ethyl oleate or ethyl elaidate gave very similar decomposition enthalpies and temperatures (Table 3, entries 4-5).[41] This preliminary study on the thermal behaviour of fatty β-hydroxy hydroperoxides shows that these oxygenated species decompose at lower temperature than the corresponding ozonides but release less energy. Interestingly, similarly than fatty ozonides, the shape of the heat decomposition of fatty β-

hydroxy hydroperoxides is very broad, indicating a gradual release of heat. For comparison, the shape of explosive azide compounds is usually very sharp and release much more energy (*e.g.*, a heat release of 1770 kJ/kg for the Zhdankin reagent, ABX).[42] The cleavage of fatty β-hydroxy hydroperoxide **2** was first studied in batch conditions (Table 4). The reaction was initially conducted in *tert*-amylalcohol at 80°C (Table 4, entry 1).

Table 4. Optimization for the thermal cleavage of fatty β-hydroxy hydroperoxide **2** in batch conditions.[a]

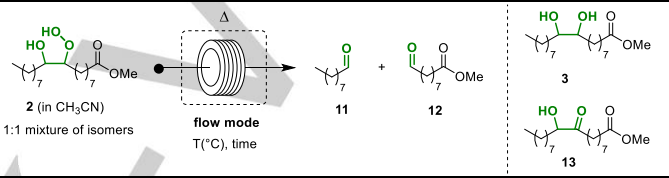


Entry	Solvent	T (°C)	Time (h)	S.[b] **11-12** (%)	S.[b] **14-15** (%)	S.[b] **3** (%)	S.[b] **13** (%)
1	t-amyl-OH	80	4	45	27	5	16
2	t-BuOH	80	4	44	12	13	20
3	CH_3CN	80	4	68	6	8	10
4	CH_3CN	60	16	76	5	5	9
5	C_2H_5CN	100	2.5	76	2	5	13
6[c]	C_2H_5CN	100	2.5	71	1	5	14
7[d]	C_2H_5CN	100	2.5	61	1	10	20
8[e]	C_2H_5CN	100	2.5	63	1	18	13

[a] Reaction conditions: 25-mL Schlenk flask, β-hydroxy hydroperoxide **2** (173 mg g, 0.5 mmol), solvent (2 mL, 0.25M). The conversion of **2** was determined by NMR and was found to be complete in all cases. [b] Selectivities were determined by GC. [c] CH_3CH_2CN (4 mL, 0.12M) was used. [d] the reaction was carried out in the presence of Amberlite-15 (10 wt%). [e] DBU (10 mol%) was used.

Under these conditions, the conversion was full after 4 hours. However, the selectivity towards aldehydes **11** and **12** only reached 45% due to the formation of acids **14** and **15** (27%), 1,2-diol **3** (5%) and α-hydroxyketone **13** (16%). A similar selectivity was obtained in *tert*-butanol but less acids and more diol were produced (Table 4, entry 2). Satisfyingly, the selectivity towards aldehydes increased to 68% when the reaction was carried out in acetonitrile (Table 4, entry 3). This selectivity was further increased to 76% when the reaction was performed at 60°C, provided a prolonged reaction time (Table 4, entry 4). More interestingly, similar results could be obtained in propionitrile at 100°C in only 2.5 hours (Table 4, entry 5). Other parameters were tested such as the concentration of substrate and the addition of acid or base catalyst (Table 4, entries 6-8). However, no improvement could be obtained under these conditions. In conclusion, the preliminary results obtained for the cleavage of β-hydroxy hydroperoxide **2** in batch conditions suggest that the selectivity of aldehydes **11-12** could be further improved by increasing the temperature. Therefore, we envisioned that the thermal cleavage could be carried out at higher temperature in a very short time, *i.e.*, working under continuous flow conditions. A solution of **2** in CH_3CN (10 g/L) was first introduced at a flow rate of 2 mL/min into an oven at 100°C (Table 5).[43] Under these conditions, the conversion only reached 20%, indicating that the reaction temperature was not high enough at this flow rate (Table 5, entry 1). Increasing the temperature from 100 to 300°C led to a 90% conversion (Table 5, entries 2-3). No attempt has been made to further increase this temperature. Doubling the concentration to 20 g/L only led to 54% conversion (Table 5, entry 4). Increasing the flow rate to 5 or 10 mL/min reduced the residence time to 36 and 18 s, respectively, thus leading to a drastic drop of the conversion (Table 5, entries 5-6). On the contrary, decreasing the flow rate to 1 mL/min gave a full conversion of β-hydroxy hydroperoxide **2** (Table 5, entry 7).

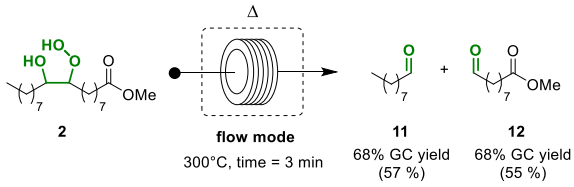
Table 5. Optimization for the thermal cleavage of fatty β-hydroxy hydroperoxide **2** in continuous flow conditions.[a]



Entry	T (°C)	Flow (mL/min)	Residence time (s)	Conv.[b] **2** (%)	Ratio[c] **11** and **12** (%)	Ratio[c] **3** and **13** (%)
1	100	2	90	20	nd	20
2	200	2	90	33	8	9
3	300	2	90	90	58	22
4[d]	300	2	90	54	14	29
5	300	5	36	10	nd	10
6	300	10	18	0	-	-
7	300	1	180	> 99	81	12

[a] Reaction conditions: β-hydroxy hydroperoxide **2** (10 g/L in CH_3CN). [b] The conversion of **2** was determined by HPLC. [c] Ratio were determined by GC. [d] [**2** in CH_3CN] = 20 g/L. *nd* = not determined.

Under these conditions, the aldehydes **11** and **12** were obtained with 81% selectivity. A reaction was performed starting from about 1 g of hydroperoxide **2** under the optimized conditions (Scheme 2). In that case, only aldehydes were obtained with 68% GC yield. These results remain satisfying considering the high volatility of such aldehydes. Purification of the mixture by column chromatography gave nonanal **11** and methyl 9-oxononanoate **12** with 57 and 55% isolated yield, respectively.



Scheme 2. Thermal cleavage of fatty β-hydroxy hydroperoxide in flow conditions. GC yield were obtained using hexadecane as an internal standard using calibration curves. Isolated yields in brakets.

This result clearly demonstrates the feasibility of a continuous flow process to prepare aldehydes from fatty epoxides through β-hydroxy hydroperoxides and paves the way for further process development.

Mechanistic considerations

In addition to its synthetic utility for the production of aldehydes from fatty β-hydroxy hydroperoxides, this work also contributes to give some insights on the reaction mechanism for the oxidative cleavage of epoxides using H_2O_2. In a recent work,[20] Lu *et al.* have proposed that the ring-opening of epoxide with H_2O_2 (1.2 equiv) in the presence of tungstic acid first produced the corresponding 1,2-diol and that this species is oxidized to either α-hydroxyketone or β-hydroxy hydroperoxide. According to our work, the formation of β-hydroxy hydroperoxide through their proposed pathway seems unlikely. In our case, the ring-opening of epoxide with aqueous 50% H_2O_2 in the presence of tungstic acid gave 93% of β-hydroxy hydroperoxide **2** and 7% of diol **3** (see Table 1, entry 4).

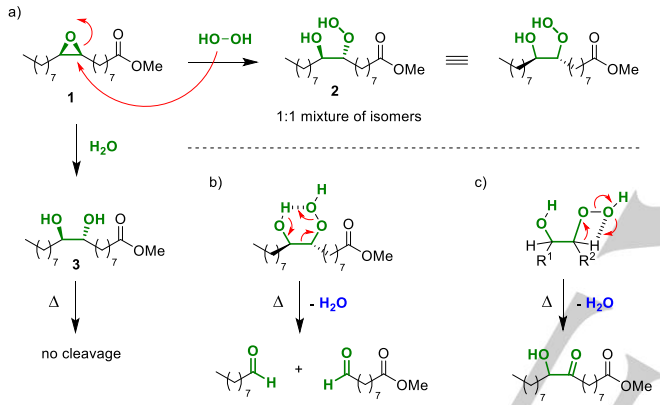


Figure 4. Mechanistic proposal for the cleavage of fatty β-hydroxy hydroperoxide to aldehydes.

This clearly demonstrates that H_2O_2 is a better nucleophile than water,[44] if not, products **2** and **3** would have been obtained in almost equimolar ratio. So, the ring-opening of epoxide **1** with aqueous 50% H_2O_2 mainly affords β-hydroxy hydroperoxide **2** as a 1:1 mixture of regioisomers (Figure 4, a). The formation of diol **3** results from the ring-opening of epoxide **1** with water as a competitive reaction. Noteworthy, diol **3** could not be thermally cleaved to the corresponding aldehydes under our reaction conditions. Moreover, no conversion of diol **3** has been obtained when treated under the same conditions than the reported systems using H_2O_2 for the ring-opening of epoxides. On the contrary, β-hydroxy hydroperoxide **2** could self-arrange in a six-membered transition state, in which the C-C bond could break upon heating, thus releasing the desired aldehydes and water as a co-product (Figure 4, b). Advantageously, both regioisomers afford the same aldehydes in this process. In addition, a molecule of water could be also eliminated from β-hydroxy hydroperoxide **2** to form α-hydroxyketone **13** as a 1:1 mixture of regioisomers (Figure 4, c).

Conclusion

In conclusion, we have developed an original method for the cleavage of fatty epoxides to aldehydes through the formation of β-hydroxy hydroperoxide intermediates. The ring-opening of epoxidized fatty derivatives with aqueous H_2O_2 in the presence of phosphostungstic acid gave a range of fatty β-hydroxy hydroperoxides with 30-80% isolated yields (8 examples). These species were fully characterized by ^1H and ^{13}C NMR, HPLC-HRMS and their stability was studied by DSC. The thermal cleavage of β-hydroxy hydroperoxides was first studied in batch conditions but higher selectivities towards the formation of aldehydes were obtained under flow conditions. Advantageously, the overall process does not require large excess of H_2O_2 and water was generated as the only byproduct. Finally, the fatty aldehydes obtained are excellent building-blocks for the production of bio-based additives (e.g., surfactants and hydrotropes) and monomers.

Experimental Section

Procedure for the preparation of fatty β-hydroxy hydroperoxides. In a 100-mL double jacketed reactor, fatty epoxide derivative (1 equiv) was added in t-amyl alcohol (2M2B; 0.25 M), phosphotungstic acid (PTA, 0.1 mol%) was added and then 1.1 equivalent of H_2O_2 (50 wt% in water) was added dropwise. The flask was closed under argon atmosphere and magnetically stirred at 10°C for 16 hours (the conversion of the epoxide was followed by GC and TLC). The reaction mixture was filtered over a celite pad and washed with ethyl acetate. The filtrate was concentrated under reduced pressure to give the crude product that was purified by column chromatography (Cyclohexane/Ethyl acetate 100:0 to 60:40).

Procedure for the thermal cleavage of fatty β-hydroxy hydroperoxides to aldehydes. A solution of β-hydroxy hydroperoxide in MeCN was prepared with a concentration of 10 g/L. The solution was pumped through an oven heated at 300°C with a flow rate between 1 to 2 mL/min. The solution of aldehydes was recovered and analyzed by HPLC (for the conversion of β-hydroxy hydroperoxide) and by GC (for the yields of aldehydes). Then, the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (cyclohexane / ethyl acetate: 100:0 to 80:20).

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Keywords: Aldehydes • Epoxides • β-Hydroxy hydroperoxides • Thermal cleavage • Flow chemistry

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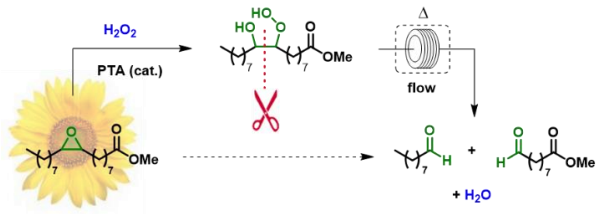
Entry for the Table of Contents



Biobased aldehydes were prepared from fatty epoxides through thermal cleavage of β-hydroxy hydroperoxide species.

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