

Alma Mater Studiorum Università di Bologna
Archivio istituzionale della ricerca

Multidecagram Scale Synthesis of an Endoperoxide, Precursor of Anti-malarial and Anti-leishmanial Agents, via Free-Radical [2 + 2 + 2] Annulation with Molecular Oxygen

This is the final peer-reviewed author's accepted manuscript (postprint) of the following publication:

Published Version:

Lardani D., Marti R., Quintavalla A., Lombardo M., Trombini C. (2021). Multidecagram Scale Synthesis of an Endoperoxide, Precursor of Anti-malarial and Anti-leishmanial Agents, via Free-Radical [2 + 2 + 2] Annulation with Molecular Oxygen. ORGANIC PROCESS RESEARCH & DEVELOPMENT, 25(12), 2718-2729 [10.1021/acs.oprd.1c00309].

Availability:

This version is available at: <https://hdl.handle.net/11585/852812> since: 2022-02-04

Published:

DOI: <http://doi.org/10.1021/acs.oprd.1c00309>

Terms of use:

Some rights reserved. The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>).
When citing, please refer to the published version.

(Article begins on next page)

This is the final peer-reviewed accepted manuscript of:

Multidecagram Scale Synthesis of an Endoperoxide, Precursor of Anti-malarial and Anti-leishmanial Agents, via Free-Radical [2 + 2 + 2] Annulation with Molecular Oxygen

D. Lardani, R- Marti, A. Quintavalla, M. Lombardo, C. Trombini

Org. Process Res. Dev. **2021**, 25, 2718–2729

The final published version is available online at:

<https://doi.org/10.1021/acs.oprd.1c00309>

Terms of use:

Some rights reserved. The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>)

When citing, please refer to the published version.

Multidecagram scale synthesis of an endoperoxide, precursor of anti-malarial and anti-leishmanial agents, via free radical [2+2+2]-annulation with molecular oxygen

Davide Lardani^a, Roger Marti^{a*}, Arianna Quintavalla^{b*}, Marco Lombardo^b, Claudio Trombini^b

^a*Institut ChemTech, HES-SO, Hochschule für Technik und Architektur, Boulevard de Pérolles 80, CH-1700 Freiburg, Switzerland*

^b*Alma Mater Studiorum, University of Bologna, Department of Chemistry "G. Ciamician", Via Selmi 2, 40126 Bologna, Italy*

*Email: Roger.Marti@hefr.ch

*Email: arianna.quintavalla@unibo.it

ABSTRACT

From screening experimental parameters to scaling up, a safe approach is reported to the multidecagram scale preparation of the methyl ester of 6,6-dibutyl-3-hydroxy-3-methyl-1,2-dioxane-4-carboxylic acid (**7**), a flexible common intermediate for the synthesis of a variety of anti-malarial and/or anti-leishmanial compounds. The critical feature of the reaction is the use of a pure oxygen flow under batch conditions using methyl acetoacetate and 2-butyl-1-hexene as reagents, and a mixture of Mn(II) and Mn(III) acetates as catalysts, in acetic acid. Once defined the best solvent, catalysts loading, temperature and reaction time in the small scale (10 mL vial), the process was adapted up to a 3 L flask, eventually resulting in the production of about 70 g of **7**. The developed reaction protocol gives a satisfactory result considering: *i*) the inexpensive starting materials used, *ii*) the 100% Atom Economy of the [2+2+2]-annulation reaction, *iii*) the stoichiometric ratio of the two reagents (only oxygen is used in excess) coupled with low catalysts loading, *iv*) the mild conditions adopted. The calorimetric studies allow us to classify this reaction as an inherently safe process. In the larger scale the possible formation of a flammable vapor mixture in the reactor headspace was minimized using two parallel continuous flows of oxygen and argon, thus ensuring a constant headspace vapor phase renewal.

KEYWORDS

Endoperoxide, [2+2+2]-free-radical annulation, three-component domino process, molecular oxygen, liquid-phase aerobic oxidation, scale-up, manganese(III)/manganese(II) catalysis

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>)

When citing, please refer to the published version.

INTRODUCTION

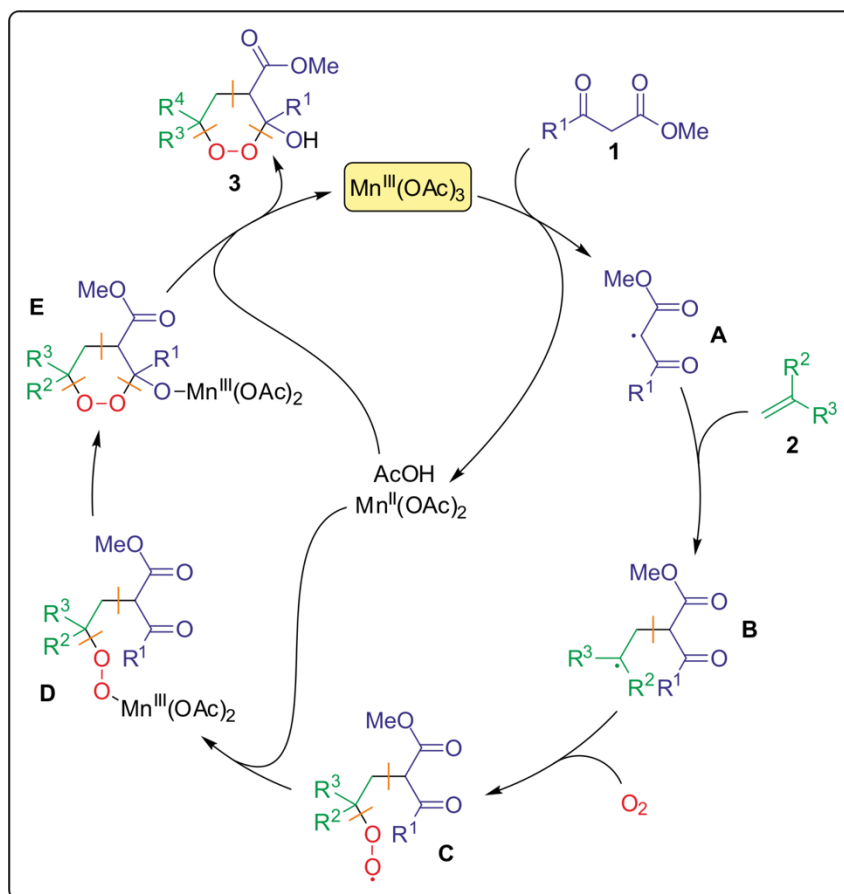
Aerobic oxidation reactions are employed in several commodity-scale chemical processes. Among the various applications in industrial chemistry, it is worth mentioning as examples the oxidation of cyclohexane to cyclohexanol,ⁱ cumene to cumene hydroperoxide,ⁱⁱ butane to maleic anhydride,ⁱⁱⁱ the Wacker oxidation of ethylene and terminal olefins,^{iv} the oxidation of para-xylene to terephthalic acid,^v up to the oxidation of primary and secondary alcohols on solid catalysts.^{vi} For all these multi-tons processes, safety protocols have been very carefully established over the years, even though the Flixborough disaster in 1974 (aerobic oxidation of cyclohexane with compressed air) is still a well-known warning in the community of industrial chemists.^{vii}

Oxidation reactions are very common in organic synthesis, however most of them are negatively affected by the poor values of their green metrics,^{viii,ix} in particular atom economy,^{x,xi} affected by a heavy formation of co-products. The use of molecular oxygen would seem to be a natural solution to this problem, mainly from a sustainability point of view.^{xii} Even if a catalyst is needed, molecular oxygen is the most atom economical oxidant, forming water as the only co-product. However, few aerobic oxidation protocols display sufficient substrate scope and selectivity, essential issues for production of pharmaceuticals. In addition to process performances, aerobic oxidation reactions in the large-scale production of chemicals are limited by the difficulties in handling O₂ on this scale, mainly because the combination of organic solvents and gaseous oxygen can represent a significant safety hazard. While in the constant production of commodities safety can be efficiently addressed, the same is too difficult in total synthesis of bioactive molecules, because of the extraordinary variability of substrates, reagents, catalysts, solvents that each synthetic plan can involve. Moreover, when toxic metal catalysts are required by the aerobic oxidation protocol, an additional problem for the pharma company is posed by rigorous regulations in terms of impurities in APIs, particularly the genotoxic ones.^{xiii,xiv}

An example of aerobic process studied in our lab at the millimolar scale over the last 10 years is reported in Scheme 1 as a general catalytic cycle.^{xv} It is based on the use of manganese salts, often employed in the field of peroxidation processes.^{xvi,xvii,xviii,xix}

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>)

When citing, please refer to the published version.



Scheme 1. [2+2+2]-Aerobic annulation of β -ketoesters and olefins.

The process, originally proposed by Nishino,^{xx,xxi} involves an oxidative interaction of Mn(III) and a β -ketoester **1** to give the enol radical **A**, which in turn adds to the *gem*-disubstituted alkene **2** leading to radical **B**. Here oxygen comes into play, delivering the peroxy radical **C**, which undergoes a reduction by Mn(II)^{xxii} to the Mn(III)-peroxide salt **D**. Ring-chain tautomerism leads to **E** and, eventually, the target peroxyhemiketal **3** is formed after protonation, regenerating the active Mn(III) species. We substantially revised the original procedure by Nishino aiming to: *i*) expand the scope of the reaction to aliphatic alkenes, besides the originally tested substituted 1,1-diarylethenes;^{xxi} *ii*) improve the process sustainability by using catalytic amounts of Mn-salts.

Product **3** is obtained as racemate, and, in the case of *gem*-disubstituted alkenes **2**, a single diastereoisomer is formed. It is characterized by the hydroxyl group at C-3 and the carbomethoxy group at C-4 in a *cis* relationship (Figure 1) and by a preferential conformation with the hydroxyl group in the axial position.^{xv} This stereoselectivity is likely due to the

stereospecific attack of the nucleophilic hydroperoxy oxygen on the ketone, determined by the stereocenter present at C-4.

Through a series of manipulations of the ester group at C4 and after ketalization at C3 with methanol, we synthesized about one hundred compounds of general structure **4** (Figure 1), differing for the G group and the R and R' substituents, but all containing the 1,2-dioxane-3-methoxy scaffold. Then, the library of endoperoxides so obtained was subjected to a campaign of bioactivity *in vitro* tests against two parasites, *Plasmodium falciparum*^{xxiii} and *Leishmania donovani*.^{xxiv} Artemisinin and other peroxy-compounds are known, indeed, to be active towards both parasites.^{xxv,xxvi,xxvii} Several endoperoxides of our library revealed promising activities as *anti-malarial*^{xxv,xxviii,xxix,xxx,xxxi,xxxii} and *anti-leishmanial* agents.^{xxxiii,xxxiv}

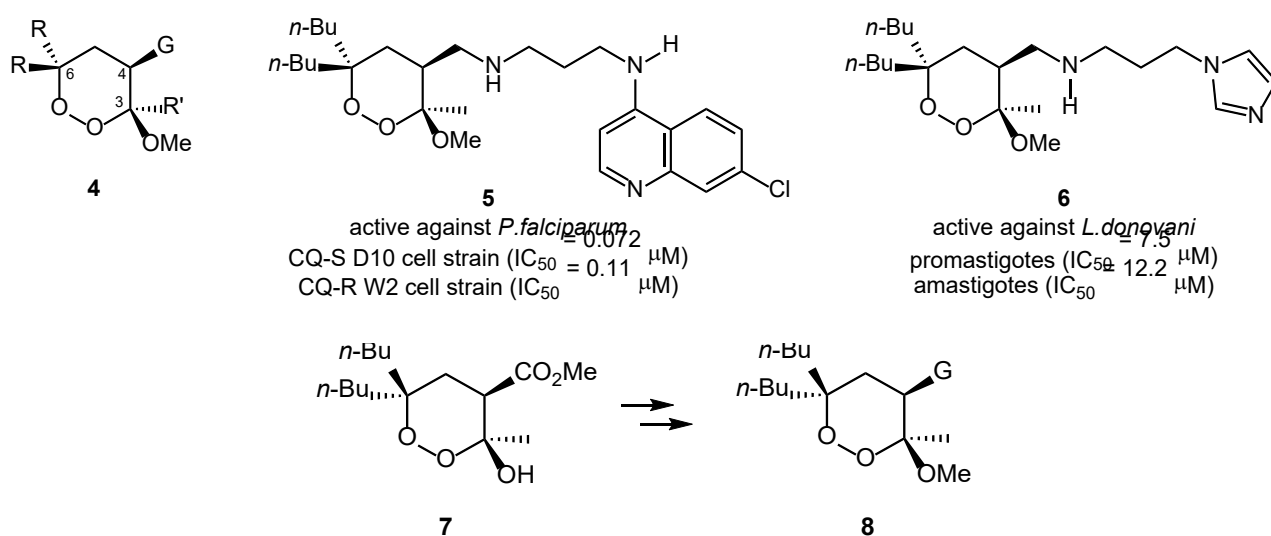


Figure 1. Bioactive 1,2-dioxane-3-methoxy derivatives synthesized by aerobic [2+2+2]-annulation (all the compounds are racemic mixtures).

Considering that compounds **5**^{xxx} and **6**^{xxxiv} (Figure 1), carrying two *n*-butyl substituents on C6 and a methyl group on C3, are among the most active endoperoxides found in our lab, we elected hemiketal **7** as the candidate of the scale-up study, being the early common intermediate both for a next generation of new molecular entities **8** with still unexplored G groups, and for *in vivo* screening of our most promising compounds (murine, rabbit, dog). While milligram amounts of products are required by *in vitro* screenings, a change of scale is necessary when addressing *in vivo* assays.

Here we present a multidecagram scale synthesis of methyl 6,6-dibutyl-3-hydroxy-3-methyl-1,2-dioxane-4-carboxylate (**7**) by aerobic [2+2+2]-annulation of 2-butyl-1-hexene (**2**) and

methyl acetoacetate (**1**), and the technical solutions adopted to ensure safety and productivity at the same time, under mild conditions.

RESULTS AND DISCUSSION

Previous preparations in the 0.25 g scale of methyl 6,6-dibutyl-3-hydroxy-3-methyl-1,2-dioxane-4-carboxylate (**7**) were carried out by adopting a procedure optimized in our lab,^{xxix} modified with respect to the original aerobic oxidation reported by Nishino, who used a stoichiometric amount of Mn salts, 3 equivalents of acetoacetate with respect to the limiting alkene, with a reaction time of 12-24 h.^{xx} In our protocol, in a 25 mL two-necked round-bottom flask equipped with a magnetic stirring bar, 2-butyl-1-hexene **2** (1 mmol) was added to a mixture of methyl acetoacetate **1** (2 equivalents), Mn(OAc)₃·2H₂O (5 mol %), and Mn(OAc)₂·4H₂O (5 mol %) in acetic acid (2 mL). The resulting heterogeneous mixture was stirred at room temperature for 4 hours under a slight overpressure of oxygen (O₂ filled balloon). The reaction is weakly exothermic, colours vary from dark orange to deep brown, then, after long standing, they turn light pink for the accumulation of Mn(II) salts coming from reduction of Mn(III) by methyl acetoacetate **1**. After neutralization with NaOH and extraction with CH₂Cl₂, **7** (219 mg, 76 %) was obtained after purification by flash chromatography.

Over a decade experience with compounds **4**, working at the 0.1-0.2 g scale with all the precautions required by potential explosive products,^{xxxv} we never faced problems with these endoperoxides. For example, hemiketal **7** was stable upon heating in boiling methanol and the corresponding methyl ketal at C3 was stable toward reducing agents like LiBH₄ and DIBAL-H, which reduce at room temperature the ester group to a primary alcohol, leaving the 1,2-dioxane ring intact. The belief that the unknown hazardous properties of endoperoxides like **7** do not require extraordinary safety standards in the 0.1-0.2 g scale was supported by the “rule of 6”. It was originally proposed for azides^{xxxvi,xxxvii} and it is an empirical guideline used to anticipate if a molecule can be considered relatively safe to handle.^{xxxviii} The condition is that the molecule presents at least six carbon atoms per energetic functionality, in our case the peroxy bond. In compound **7** the ratio between number of carbon atoms and number of energetic functionalities is 16, much higher than the safety limit of 6. Moreover, the anomalous stability of endoperoxides possessing a further oxygenated carbon in the α-position, being an acetal, a ketal, or a further peroxide group (bis-peroxides such as tetraoxanes), has been recently rationalized.^{xxxix} Indeed, a strong stabilizing anomeric interaction, lacking in an isolated endoperoxide, is activated by

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>)

When citing, please refer to the published version.

introducing in the α -position a suitable sigma-acceptor orbital (σ^* of C-O, C-N, or C-F bonds), making the peroxide bond considerably stronger.

On this basis, we sought to scale up the reaction by 500 times, with the aim to produce more than 70 g of **7** in a single batch. The first issues under investigation were: *i*) the hazards associated to the reaction scale, considering that the headspace of the reactor could contain a flammable atmosphere, and *ii*) the thermal stability of **7** for a safe handling and storage.

Safety Issues related to Molecular Oxygen.

The major alarm in industrial oxidations, caused by the use of a pure oxygen atmosphere, is the formation of a flammable vapor phase in the reactor headspace, that could in principle lead to an explosion in the presence of an ignition source, such as a spark or flame.^{xi} The worst-case scenario happens when the organic components of the vapor phase, essentially composed of the solvent and the most volatile reagents/products, are present in a critical concentration in the presence of oxygen,^{xii} with an inadequate elimination of all possible ignition sources. The problem is extremely critical when working at high pressure and temperature, where minimum ignition energies are ever lower, and a reliable prevention of ignition sources is difficult. To ensure safe operations, a practical approach, proposed by Osterberg and co-workers, is to operate below the limiting oxygen concentration (LOC) for the organic solvent and/or reagents used in a chemical reaction.^{xiii} LOC is the minimum O₂ concentration in a mixture of fuel, air, and an inert gas, below which combustion is not possible. Unfortunately, there is a scarcity of published flammability data for common organic solvents. Osterberg measured the LOC value of acetic acid in the presence of nitrogen at 200 °C. He found that the LOC at 1 bar was identified at an acetic acid concentration of 7.3 vol % and 10.6 vol % of oxygen. However, these conditions are very far from the reaction protocol we want to adopt, that works nearly at room temperature (very low solvent vapor pressure) and with no overpressure.

The reason to use pure oxygen is due to the poor solubility of O₂ in acetic acid, the most commonly used solvent in the manganese(III)-acetate promoted syntheses.^{xiii} Recent experimental data report that the molar fraction x of O₂ in acetic acid at 0.162 MPa and 293 K corresponds to 6.8×10^{-4} , with the Henry coefficient for oxygen in acetic acid = 242.5 MPa.^{xiv} Poor solubility makes the rate of oxygen mass transfer from the gas phase to the liquid phase a rate determining factor. In addition, oxygen solubility is dependent on the interfacial contact area between the gas and liquid phases. It can be easily demonstrated on pure geometric grounds that, increasing the batch reactor size, the gas–liquid interfacial area to volume ratio considerably decreases, thus making difficult to reproduce a small-scale reaction into a bigger reactor. Considering a 25 mL and a 250 mL round bottom flasks, the

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>)

When citing, please refer to the published version.

half-height radius doubles from 0.021 to 0.043 m, and consequently the interfacial area to volume ratio halves from 71 to 35 m⁻¹.^{xlv}

In scaling up studies, we ruled out any reactor pressurization to maximize the amount of oxygen in solution, for obvious safety reasons. Instead, we found a good trade-off between reactivity and safety by adopting a two parallel gas inlets configuration. Oxygen is bubbled through the solution, since it is known that mass transfer in gas-liquid systems is speeded up in a rising bubble.^{xlvi} Secondly, we kept clean the reactor headspace by a constant inflow of argon. Argon, denser than oxygen and nitrogen, is more efficient in purging the liquid-gas headspace, ensuring a constant vapor phase renewal.

Preliminary Screenings in the Lab Scale.

Reproducibility.

First, we screened the reproducibility of the preparation of **7** under oxygen flow (no O₂ filled balloon) at the lab scale. A 10 mL vial equipped with a overturnable pierceable silicon septum and a magnetic stirring bar was charged with 2-butyl-1-hexene **2** (281 mg, 2 mmol), methyl acetoacetate **1** (0.432 mL, 4 mmol), acetic acid (4 mL), Mn(OAc)₃·2H₂O (26.8 mg, 5 mol %), and Mn(OAc)₂·4H₂O (24.5 mg, 5 mol %). Oxygen was slowly bubbled inside the solution from a balloon through a needle, while a second needle reaching the headspace works as vapor phase vent (Figure 2).

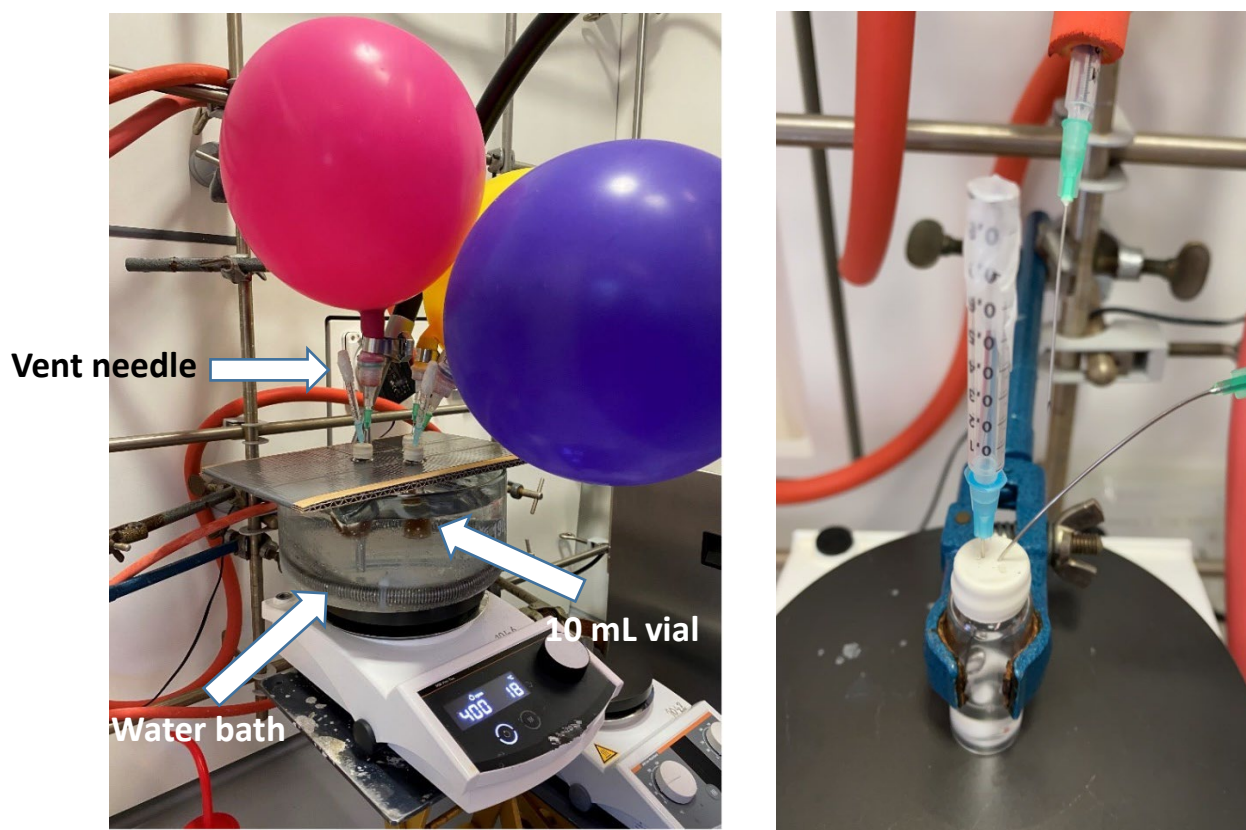


Figure 2. Oxygen bubbling in the small scale laboratory equipment (double needle technique).

The mixture was stirred at 23 °C for 4 hours. In a triplicate experiment, the purified yield of **7** was 57 ± 7 %. The critical points that make rather high the yield fluctuation can be due in part to a possible and variable loss of reagents in the vapor stream,^{xlvii} in part to the work-up procedure which involves acetic acid neutralization with NaOH 6M, extraction and flash-chromatography.

Being an open system, it is not possible to carefully evaluate the reaction conversion due to a probable loss of part of the limiting alkene, which in any case is observed in trace amount in the ^1H -NMR spectrum of the crude extract after NaOH neutralization, extraction and evaporation at reduced pressure. Moreover, the alkaline neutralization might be responsible for the absence in the crude extract of traces of methyl acetoacetate, which is likely present in the alkaline aqueous phase as the corresponding enolate. In general, the crude extract mainly consists of **7**, being the Nishino side-product (namely methyl 5,5-dibutyl-4,5-dihydrofuran-3-carboxylate) less than 5 % in the ^1H -NMR spectrum.

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>)

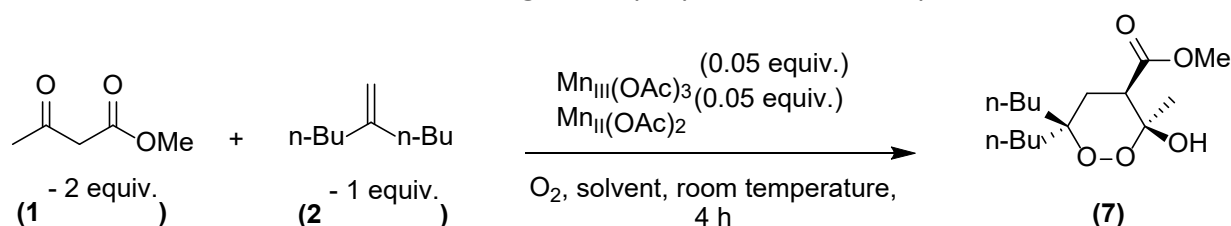
When citing, please refer to the published version.

Afterwards, for obvious safety principles, we checked the reaction response to the use of dry air^{xxi,xlviii,xlix} instead of pure oxygen. We ran two parallel experiments on 2 mmol scale and the yield of the purified product **7** using dry air was 35 %, while using pure oxygen was 54 %. These results confirmed that the amount of dissolved oxygen plays a crucial role in determining the performance of the transformation. Considering the significant gap, we continued our process development using pure oxygen.

Solvent Screening.

The solvent plays a relevant role in the Mn(III)-based oxidative reactions.^{i,li,liv,lvi} In our case, the solvent, beside to be compatible with a free-radical process, must dissolve oxygen^{liv,lv} and solubilize at least in part the Mn salts. In addition, an acidic solvent can contribute to: *i*) restore the catalyst by protonation of the hemiketal **E** (Scheme 1), *ii*) enhance the condensation rate between the enol-radical **A** and the olefin **2** (Scheme 1),^{lvi} *iii*) increase the oxidising capacity of Mn(III)-acetate,^{lvii,lviii} *iv*) participate in controlling the solubility and the oxidation state of the Mn-species.^{lix} On this basis, we screened different acidic solvents beside to acetic acid (pKa = 4.7 in H₂O). In particular, we tested formic acid (pKa = 3.8), a 1:1 mixture of acetic and formic acid, propionic acid (pKa = 4.9), hexafluoroisopropanol (HFIP, pKa = 9.3), trifluoroethanol (TFE, pKa = 12.5), trifluoroacetic acid (TFA, pKa = 0.5) and methanesulfonic acid (MsOH, pKa = -1.9). We included fluorinated solvents for their ability to dissolve oxygen.^{lx,lxi} Reaction conditions were identical to those previously reported using acetic acid.

Table 1. Solvent screening in the preparation of endoperoxide **7**.



Solvent	pKa	Quantitative ¹ H NMR-Yield % ^a
AcOH	4.7	50
HCOOH	3.8	43
AcOH:HCOOH = 1:1 (V/V)		24
Propanoic acid	4.9	40
HFIP	9.3	42
TFE	12.5	25

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>)

When citing, please refer to the published version.

TFA	0.5	No product ^b
MsOH	-1.9	No product ^b

Reaction conditions: 2-butyl-1-hexene **2** (2 mmol), methyl acetoacetate **1** (4 mmol), solvent (4 mL), Mn(OAc)₃·2H₂O (5 mol %), Mn(OAc)₂·4H₂O (5 mol %), O₂ (flow using double needle technique), room temperature, 4 h. ^a Determined by ¹H NMR spectroscopic analysis of the crude mixture using 1,4-dimethoxybenzene as internal standard and integrating the signals of the product. ^b Complex crude mixture. equiv. = equivalents.

Among this solvent list, the most acidic ones did not provide the expected product, however it seemed that an upper pK_a threshold does not exist, since also HFIP and TFE promoted the radical cascade outlined in Scheme 1. However, if a benefit came from the high solubility of oxygen in HFIP (mol fraction = 16.37×10^{-4} at 283 K and 1 atm) and TFE (mol fraction = 9.29×10^{-4} at 283 K and 1 atm)^{lxii} compared to acetic acid (mol fraction = 6.8×10^{-4} at 293 K and 1.5 atm),^{xliv} this was counterbalanced by the poorer solubility of manganese salts. It is also interesting to notice the trend going from formic to propanoic acid, with a maximum yield corresponding to acetic acid, that in this way resulted the solvent of choice.

In order to define the best reaction medium, safety and toxicity were also compared^{lxiii} using a laboratory risk assessment (LRA) model^{lxiv, lxv, lxvi, lxvii} (see Supporting Information). Considering reaction performance (yield), cost and safety/toxicity, the obtained results confirmed acetic acid as the best reaction medium.

Reaction Time Optimization.

Three reactions were conducted in parallel, using the same parameters but varying the reaction time (Table 2). After introducing solvent, catalysts and the two reagents, t = 0 did correspond to the oxygen flow start. Then, the oxygen flow was interrupted after a precise time, the usual work-up was performed and internal standard was introduced in the reaction mixture, followed by quantitative ¹H NMR yield (q¹H NMR-Y) determination and purification of the product.

Table 2. Effect of the reaction time on the chemical yield.^a

Reaction time (hours)	q ¹ H NMR-Y (%) ^b	Isolated yield % ^c
2	35	30
3	52	50
4	56	52

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>)

When citing, please refer to the published version.

^a Reactions carried out on 2 mmol scale of 2-butyl-1-hexene **2** as limiting reagent. ^b Determined by ¹H NMR spectroscopic analysis of the crude mixture using 1,4-dimethoxybenzene as internal standard. ^c Purification performed by flash-chromatography.

These results demonstrated that reaction times of 3 or 4 hours provided comparable reaction outcomes and this is a good point in terms of productivity. Moreover, it is important to highlight the good match between quantitative ¹H NMR yield and isolated yield, confirming a very good reliability of the yield determination by NMR and a very limited loss of product in the purification stage in the small scale.

Although the yields previously obtained in a closed reactor were higher,^{xxix} these results showed that good yields can also be obtained in an open system (double needle technique), which has significant advantages in terms of process safety and offers good prospects for the process scale up.

Optimization of Catalyst Loading, Temperature and Reagents Molar Ratio.

A design of experiments (DoE)^{lxviii, lxix, lxx} was carried out to optimize the title parameters. We created a design matrix shown in Table 3 for the three factors being investigated with three levels for each input factor, chosen as most relevant on the basis of our previous experience.

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>)

When citing, please refer to the published version.

Table 3. Design matrix for temperature, reagents molar ratio and catalyst loading.^a

T (°C)	Catalysts (equiv.)	Reagents ratio (equiv.)	q ¹ H NMR-Y %	Y %
11	0.025	1	3.5	-
		1.5	7.0	-
		2	8.1	-
	0.05	1	3.5	-
		1.5	5.2	-
		2	8.9	-
	0.075	1	3.2	-
		1.5	5.6	-
		2	8.3	-
23	0.025	1	47.8	46.5
		1.5	65.8	63.7
		2	47.1	48.5
	0.05	1	50.1	48.8
		1.5	68.6	65.7
		2	64.2	61.7
	0.075	1	39.2	40.3
		1.5	44.1	45.1
		2	52.1	49.2
40	0.025	1	70.1	66.8
		1.5	75.0	69.3
		2	71	67.9
	0.05	1	59.1	56.5
		1.5	60.3	57.2
		2	67.1	64.7
	0.075	1	48.2	48.5
		1.5	62.8	62.4
		2	67.5	64.2

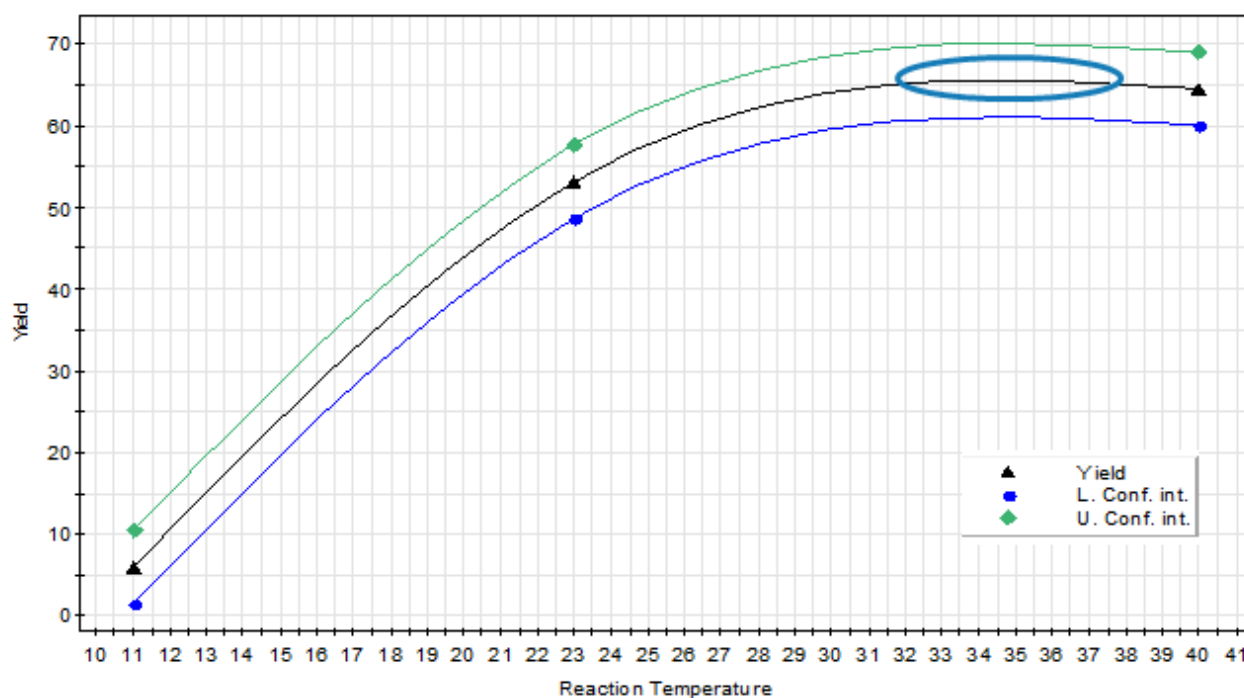
^a Reactions carried out on 2 mmol scale of 2-butyl-1-hexene **2** as limiting reagent. Reagents ratio = mmol of **1**/mmol of **2**. q¹H NMR-Y % determined by ¹H NMR spectroscopic analysis of the crude mixture using 1,4-dimethoxybenzene as internal standard. Y % determined after purification performed by flash-chromatography.

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>)

When citing, please refer to the published version.

Concerning temperature and catalysts loading, the previously employed conditions (23 °C and 0.05 equivalents, respectively) were considered as middle values in the design matrix, therefore some experiments were carried out using higher or lower values for these parameters. Conversely, aiming to improve the process sustainability, the previously reported excess of methyl acetoacetate **1** (2 equivalents) was reduced. The response of each experiment, among the 27 performed, was the quantitative ^1H NMR-Yield (q ^1H NMR-Y). Moreover, the 18 crude mixtures showing acceptable yields were purified, providing the corresponding purified yield values. The evaluation of the experimental findings and the statistical analysis of the 27 experiments, performed with the DoE software package MODDE 9 (see Supporting Information for details), led us to the following conclusions.

Temperature plays a remarkable role in this reaction as shown in Table 3. Lowering the temperature led to a heavy decrease of the yields regardless of the value of the other parameters. This is likely due to the poorer catalyst solubility in these conditions. Moving from 23 to 40 °C we observed a general yield increase. However, it is interesting to note that the most relevant improvement (70-75 % yield) was recorded in the presence of the lowest catalyst loading (2.5 mol %). The statistical analysis of the DoE results provided a model that, interestingly, anticipates higher yields in the temperature range from 33 to 38 °C (Figure 3). This forecast is also in accordance with the trend of oxygen solubility with temperature (Henry coefficient of oxygen in acetic acid decreases with increasing temperature).^{xliv}



This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>)

When citing, please refer to the published version.

Figure 3. Model expected yield based on reaction temperature.

Regarding the amount of catalysts used, we already mentioned that, the highest yields (70-75 %) were obtained using the smallest amount of catalysts (0.025 equivalents). In addition, at both 23 and 40 °C, an increase of the catalysts loading from 5 to 7.5 mol % did not provide a significant yield improvement.

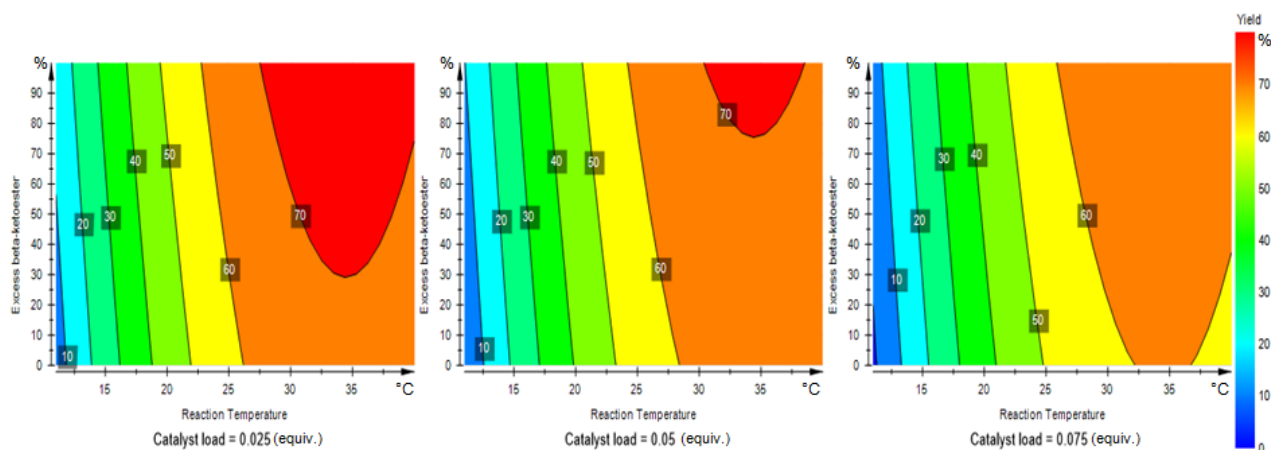


Figure 4. DoE contour plots.

The contour plots in Figure 4 show the yields (low yield, blue; high yield, red) as a function of the three factors (temperature, catalysts loading and methyl acetoacetate equivalents) used in the DoE matrix design. The three contour plots refer to three different catalysts loadings. The experimental findings and the result proposed by the model are noteworthy since the catalysts amount is not directly proportional to the product yield. The observed peculiar behavior might be caused by: *i*) catalysts promoting side-reactions, *ii*) catalysts not completely soluble. Further studies should be carried out to confirm the effects of catalysts load on the yield.

Analyzing the stoichiometry of the reagents **1** and **2**, it can be seen that the highest yields were obtained with an excess of the β -ketoester **1** (1.5 or 2 equivalents with respect to limiting alkene **2**). This makes sense since the use of an excess of a reagent (in this case the cheapest one) can obviously favor the reaction kinetics. Moreover, an excess of the oxidizable substrate might help to avoid a possible competitive oxidation of the reaction product.^{lxxi} In fact, most of the Mn-based protocols furnishing endoperoxides involve a large excess of β -ketoester.^{lxxii, lxxiii, lxxiv, lxxv} In our case, it is noteworthy that the best result (75 % yield) was obtained employing only a slight excess of methyl acetoacetate (1.5 equivalents). The model derived from the DoE study indicates that the excess of β -ketoester **1** does not

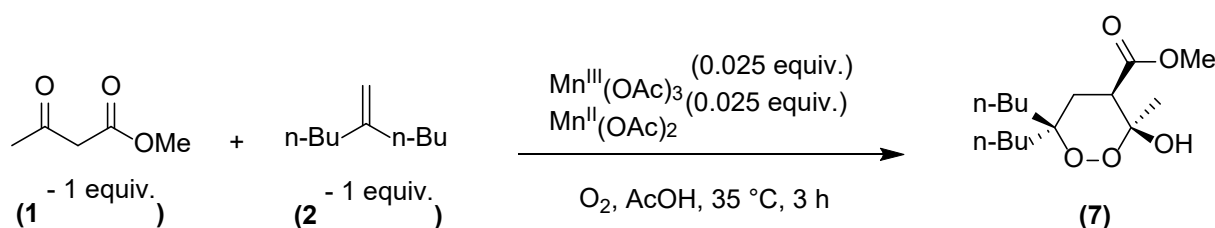
have relevant consequences on the reaction outcome, therefore we decided to proceed with the reaction scale up employing only one equivalent of substrate **1** aiming to decrease the process costs, mass intensity and to facilitate the product purification.

Summarizing this part, the DoE results and the derived model highlighted some features of the studied transformation that can be crucial in terms of process sustainability and scale up. Indeed, the best performance was achieved employing a quite low catalysts loading (2.5 mol %), in the presence of a moderate excess of methyl acetoacetate (1.5 equivalents) and working at a temperature ($32 \leq T \leq 37$ °C) just above the room temperature, that is easily reachable in energy terms.

As a further remark, the DoE results confirmed the very good agreement between quantitative ^1H NMR yield and purified yield, therefore demonstrating a limited impact of the purification step in the small scale.

Multidecagram Preparation of Endoperoxide **7**.

On the basis of the previously described results, we proceeded with the process scale up. Our scaling up experiments ranged from a 100 mL flask, through a 1 L and finally to a 3 L reactor, using the reaction conditions shown in Scheme 2.



Scheme 2. Reaction conditions in the preliminary scaling up studies.

Pursuing efficiency, we adopted the best conditions found in the preliminary screening, as refers to catalyst loading, solvent, temperature and reaction time, while a 1:1 reagents ratio was preferred to more unbalanced ratios given the negative impact of any excess reagent on the green metric factor defined as Process Mass Intensity.^{lxxvi} Oxygen is bubbled, directly from a cylinder through a mass flow controller, inside the reaction mixture through a gas dispersion fritted glass tube that minimizes the bubbles size (Figure 5).



Figure 5. 1 L reaction set-up.

The main problem now is to minimize the formation of potentially ignitable flammable vapours in the reactor headspace. To this purpose, argon^{lxxvii, lxxviii} was constantly introduced by an independent inlet into the headspace, with a flow about 3 times higher than that of oxygen (0.1 L/min), to dilute and remove the vapours through the condenser connected to a bubble counter into the exhaust ductwork of the fume hood.

The third scaling up experiment in a 3 L jacketed cylindrical glass reactor required additional care. An external thermostat ensured a careful temperature control during the heating/cooling operations thanks to a heat transfer fluid circulating in the jacket (Figure 6).

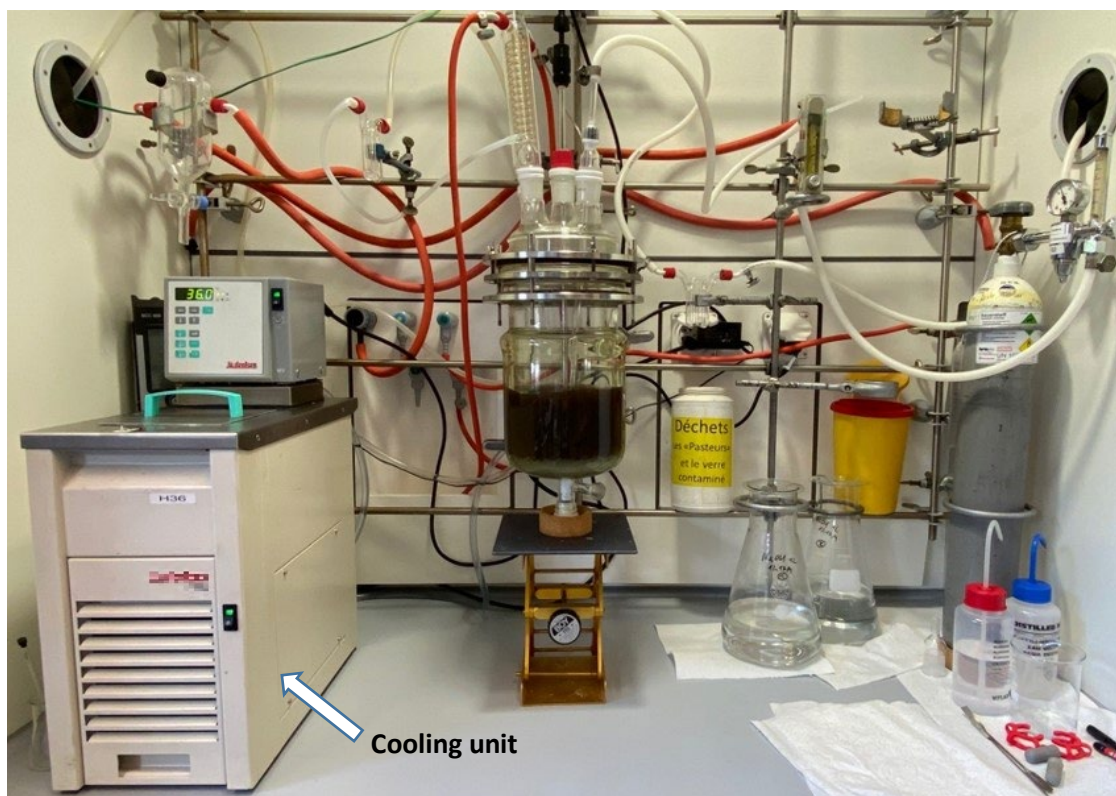


Figure 6. 3 L reaction set-up.

Magnetic stirring cannot be used for this reactor, so a mechanical stirrer was installed. To improve mixing, an impeller pitched-blade helix with axial flow pattern was used (see Supporting Information). For the independent inlets of oxygen and argon and for the overpressure release, the system previously discussed was readapted.

Using the 1 L reactor we were delighted by a 60 % yield of purified endoperoxide **7** (42.34 g, 147 mmol). This result is in line with those obtained in the DoE study (Table 3) on the small scale (2 mmol) at 35 °C.

The reaction in the 3 L reactor was performed twice, obtaining a maximum yield of 50 % (77.7 g, 250 mmol of purified endoperoxide **7**). The yield drop might be due to the changes in reactor geometry and stirring system. Anyhow, by bubbling oxygen directly into the reaction mixture, a small part of the solvent and reactants evaporates and is removed from the reaction mixture. The impact of this phenomenon might be greater in the 3 L reactor than in 1 L reactor. However, although the use of an open system coupled with an inert gas flow may have some disadvantages, this batch approach allows to maintain a safely purged reactor headspace during the reaction progress.

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>)

When citing, please refer to the published version.

Calorimetric Studies.

Adiabatic tests are widely used in the risk assessment of chemical processes. Adiabatic conditions by definition do not allow the exchange of energy between a reaction system and the environment. The adiabatic temperature rise of a chemical reaction (ΔT_{ad}), namely the maximum increase in temperature that can be achieved under adiabatic conditions, is a function of the reaction enthalpy and the reaction rate. The higher it is, the higher is the thermal hazard of an exothermic reaction in the worst scenario of failure of the cooling system.^{lxxix}

We, thus, investigated the ΔT_{ad} of the [2+2+2]-annulation reaction using an EasyMaxTM 102 instrument. The determined ΔT_{ad} corresponds to 2.2 K (see Supporting Information), which allows us to classify this reaction as an inherently safe process. To complete the calorimetric studies, differential scan calorimetry (DSC) analysis of endoperoxide **7** was performed (Figure 7). The endoperoxide decomposition peak presents the maximum value at 195 °C and an onset temperature of 160 °C. The total heat released by the decomposition corresponds to 743.6 J/g, a high value as expected for a molecule containing a weak O-O bond. However, the onset temperature and decomposition peak are quite high in comparison to other organic peroxides.^{lxxx, lxxxi, lxxxii, lxxxiii, lxxxiv, lxxxv} In light of process scalability and safety assessment, we decided to study in more depth the decomposition behavior of the endoperoxide **7**. In fact, its decomposition likely starts at a temperature (defined as “left limit”, around 100 °C in Figure 7) lower than the onset temperature. Considering that the cycloaddition proceeded at 35 °C, we performed an isothermal DSC analysis at 90 °C (reaction temperature + 50 °C) for 10 hours (see Supporting Information), which demonstrated the complete stability of the endoperoxide **7** at this temperature and ensuring a safe process.

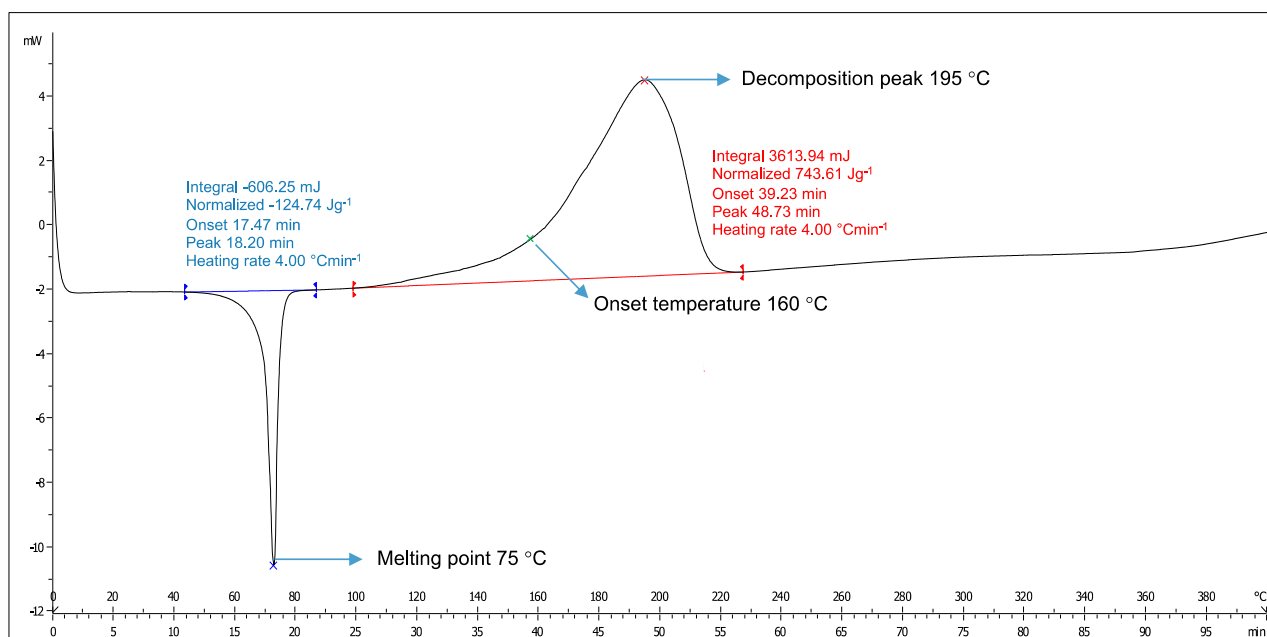


Figure 7. Differential Scan Calorimetry (DSC) analysis of endoperoxide **7**.

Two conclusions can be drawn from calorimetric studies: *i*) being ΔT_{ad} so smaller than both the onset temperature and the “left limit” temperature, the [2+2+2]-cycloaddition is thermally safe, and *ii*) explosive hazards of handling and shipping methyl 6,6-dibutyl-3-hydroxy-3-methyl-1,2-dioxane-4-carboxylate **7** are very limited if temperature is kept below the precautionary threshold of 100 °C.

Ultimately, the major safety issue of the large-scale preparation of endoperoxide **7** is the use of a reactive and oxidizing gas like oxygen.

CONCLUSION

This study demonstrates that the process leading to compound **7** through a [2+2+2]-cycloaddition of an alkene, a β -ketoester and molecular oxygen can be considered an inherently safe process in terms of thermal hazard. The high number of possible simple starting materials combined to the variety of possible late-stage structural manipulations make endoperoxides **3** appealing intermediates for the generation of libraries of useful products. These synthetic approaches have been limited, so far, by the potential hazards connected to the use of pure oxygen, the main limitation in view of a larger scale preparation of these compounds. Despite the beautiful properties of molecular oxygen as reactant (it is inexpensive, environmentally benign, and its reactions often display high atom economy),^{lxxxvi} the combination of this oxidizing agent and organic molecules always implies the hazard of runaways and explosions. Here we present the developed multidecagram scale

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>)

When citing, please refer to the published version.

synthesis of endoperoxide **7** via [2+2+2]-annulation with molecular oxygen under safety-controlled conditions. In the larger scale the possible formation of a flammable vapor mixture in the reactor headspace was minimized using two parallel continuous flows of oxygen and argon, thus ensuring a constant headspace vapor phase renewal. In the future, the use of pure oxygen, often preferred over “synthetic air” in terms of yield, selectivity, productivity, and product quality, might be addressed through the utilization of the continuous-flow technology,^{xl, lxxxvii, lxxxviii} with the aim of further increasing the process productivity while maintaining safe operating conditions. The precise temperature control, the small channel dimensions which provide a high surface-to-volume ratio enabling a quick heat dissipation, the large interfacial area between gas and liquid that minimizes mass-transfer effects, the possibility to easily pressurize, thus increasing the solubility of oxygen, are all factors that would favour the adoption of flow chemistry for a safe and efficient pure oxygen handling at the industrial scale. However, work is needed to apply flow chemistry also at the decagram scale reported in this study, mainly because of the multiphase nature of the reaction mixture where two partially soluble manganese salts are present as catalysts, not easily dockable to inert supports. Work in this direction is in progress and it will be reported in due course.

EXPERIMENTAL SECTION

General Information. All reagents and solvents used are commercially available from Sigma-Aldrich, Alpha Aesar, Acros Organics, abcr Gute Chemie, Carl Roth, Thermo Fisher Scientific, Brunschwig Chemie and were used without further purification, except 2-butyl-1-hexene (**2**), which was synthesized in the laboratories of the “Haute école d'ingénierie et d'architecture” of Fribourg. All reactions were monitored by thin layer chromatography (TLC) on aluminium plates coated with silica gel 60 F254 plates (0.25 mm) and observed under an UV lamp (254 and 366 nm). The synthesized compounds were characterized by ¹H (300 MHz) and ¹³C (75 MHz) NMR spectroscopy using a Bruker 300 Ultra ShieldTM and chloroform-d with TMS was used as solvent. 1,4-Dimethoxybenzene was used as internal standard to evaluate the quantitative ¹H NMR-Yield (q¹H NMR-Y). Spectral assignments were supported by APT, COSY (45), HSQC. Chemical shifts values are given in parts per million (ppm) considering the residual non-deuterated solvent as reference, and the coupling constants *J* are given in Hertz (Hz). The multiplicities of ¹H signals are indicated as: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (double doublet). Infrared spectra (IR) were recorded on Bruker ALPHA. Melting and boiling points were determined with a BUCHI Melting Point M-560. Synthesized compounds were also characterized by mass spectrometry, performed with an

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>)

When citing, please refer to the published version.

electrospray-ionization mass spectrometer (ESI-MS) Waters SQD2. The thermal analyses were performed with EasyMaxTM 102 and a Mettler DSC 2 STAR^e System. The elemental analysis was performed with Flash 2000 Organic Elemental Analyzer by Thermo ScientificTM using the universal Soft Tin Container (diameter: 5 mm; high: 8 mm; volume: 157 μ L) by Thermo ScientificTM. The standard used as reference was 2,5-bis(5-tert-butyl-2-benzoxazol-2-yl) (BBOT) with certificate number of analysis for standard and reference material of 202147.

2-Butyl-1-hexene (2).

In a round three-collar flask, $\text{Ph}_3\text{PCH}_3\text{Br}$ (30 mmol, 10.93 g) and anhydrous THF (370 mmol, 30 mL) were added under slight N_2 flow (inert atmosphere). The solution was stirred taking a white color. Then, after placing the flask in an ice bath, $n\text{-BuLi}$ (1.6 M in hexane, 30 mmol, 20 mL) was added dropwise. The solution turned to an orange-red color. When the dropping was complete, the ice bath was removed and the solution was allowed to reach room temperature. After 30 minutes of stirring, a solution of 5-nonanone (27 mmol, 4.77 mL) in anhydrous THF (136 mmol, 11 mL) was added dropwise. The solution slowly changed color to light yellow. Once dropping was complete, the mixture was stirred at room temperature overnight. Then, the solution was decanted in an ice bath for 30 minutes and filtered under vacuum using a Büchner funnel with a fritted glass disc (pore size G4) and 1 cm of silica to remove Ph_3PO . The solid Ph_3PO was washed with cold cyclohexane. The obtained transparent liquid was concentrated under reduced pressure (water bath temperature below 50 °C). The presence of the product and any traces of unreacted ketone and/or Ph_3PO was checked by TLC (mobile phase 90% cyclohexane - 10% ethyl acetate, product $R_f = 0.9$). When traces of unreacted 5-nonanone were present, flash chromatography with 100% cyclohexane as mobile phase provided the pure product (**2**). Yield = 70%, colorless liquid. **ESI-MS:** m/z 163 $[\text{M} + \text{Na}]^+$. **¹H NMR** (300 MHz, CDCl_3 with TMS): $\delta = 0.91$ (t, $J = 7.1$ Hz, 6 H, 2 x CH_3), 1.26 - 1.44 (m, 8H, 4 x CH_2), 2.00 (t, $J = 7.2$ Hz, 4H, 2 x CH_2), 4.68 (s, 2H, CH_2). **¹³C NMR** (75 MHz, CDCl_3 with TMS): $\delta = 150.4, 108.2, 35.8, 30.0, 22.5, 14.0$. **Boiling Point** (°C) = 170,36 \pm 0,73. **IR** (cm^{-1}): ν 2859-2956 (stretching C-H), ν 1378-1456 (bending C-H), ν 1644 (stretching C=C).

Methyl 6,6-dibutyl-3-hydroxy-3-methyl-1,2-dioxane-4-carboxylate (7).

Small scale procedure (10 mL-flask; reproducibility study, solvent screening, time optimization, DoE study):

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>)

When citing, please refer to the published version.

A 10 mL vial equipped with a overturnable pierceable silicon septum and a magnetic stir bar was charged with 2-butyl-1-hexene **2** (281 mg, 2 mmol), methyl acetoacetate **1** (0.432 mL, 4 mmol), acetic acid (4 mL), $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ (26.8 mg, 5 mol %), and $\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (24.5 mg, 5 mol %). Oxygen was slowly bubbled inside the solution from a balloon through a needle, while a second needle reaching the headspace works as vapor phase vent. The mixture was stirred at 23 °C for 4 hours.

In the solvent screening, acetic acid was replaced by other solvents (see Table 1).

Aiming to optimize the reaction time, the mixture was stirred for different times (see Table 2).

In the DoE study, the equivalents of methyl acetoacetate (**1**), the temperature and the catalysts loading were varied (see Table 3).

Reaction quenching was performed with 6 N NaOH, slowly added to the solution inside the vial, placed in an ice bath. The pH was monitored with litmus paper until neutral (~7). The reaction mixture was then extracted using AcOEt (3x20 mL) and the organic phase was washed with NaHCO_3 (saturated solution, 3x20 mL). The organic phase was dried with Na_2SO_4 , then filtered with cotton ball in glass funnel. The solvent was removed under vacuum. All crude extracts were purified using a CombiFlash automated chromatographic system (see Supporting Information) and cyclohexane / AcOEt 8:2 V/V as eluent. The final product is a white solid. TLC: R_f = 0.5 (80% cyclohexane - 20% ethyl acetate). **ESI-MS**: m/z 311 $[\text{M} + \text{Na}]^+$. **^1H NMR** (300 MHz, CDCl_3 with TMS): δ = 0.85 (q, J = 6.9 Hz, 6H, $2 \times \text{CH}_3$), 1.37 - 1.05 (m, 12 H, $6 \times \text{CH}_2$), 1.42 (s, 3H, CH_3), 1.68 (dd, J = 14.0, 5.0 Hz, 1H, CH), 2.03 (t, J = 14.0, 13.0 Hz, 1H, CH), 2.85 (dd, J = 13.1, 5.0 Hz, 1H, CH), 3.67 (s, 3H). **^{13}C NMR** (75 MHz, CDCl_3 with TMS): δ = 13.9, 14.1, 23.1, 24.3, 24.8, 25.5, 30.6, 31.0, 36.2, 44.6, 52.1, 81.4, 97.9, 172.3. **Melting Point** (°C) = 75 ± 0.52 . **IR** (cm^{-1}): ν 3440 (stretching O-H), 2949-2935-2870 (stretching C-H), 1733 (stretching C=O), 1158 (stretching C-O), 1075 (stretching C-O-O-C), 849 (stretching O-O). **Elemental Analysis**: calcd for $\text{C}_{15}\text{H}_{28}\text{O}_5$: C, 62.47; H, 9.79. Found: C, 62.42; H, 10.31.

Small scale procedure (100 mL-flask):

In a three-necked round bottom flask $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ (0.625 mmol, 0.18 g), $\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (0.625 mmol, 0.16 g) and glacial acetic acid (865 mol, 50 mL) were added. The mixture was stirred for about 20 minutes at 35 °C with a magnetic stir bar to promote the catalysts dissolution. Then, the reagents were added in the following order: 2-butyl-1-hexene (**2**) (25 mol, 3.5 g), then methyl acetoacetate (**1**) (25 mol, 2.7 mL). The mixture was stirred for 10 minutes at 35 °C. To monitor the temperature during the reaction, a temperature probe was

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>)

When citing, please refer to the published version.

fitted into one of the three reactor necks. Finally, a constant flow of oxygen was introduced into the mixture using a needle connected to a plastic balloon. For this reaction, a reflux condenser linked to a bubble counter was installed in the central neck of the flask, which served as oxygen vent. The reaction was stirred for 3 hours at 35 °C. The product formation was monitored by TLC after one and two hours from the oxygen addition. After 3 hours, the flask was placed in an ice bath and the acidic mixture was slowly quenched with NaOH (10 M) until neutral pH. The solution was extracted with AcOEt (3 x 40 mL) and the organic phase was washed with NaHCO₃ (saturated solution, 3 x 40 mL). The organic phase was dried on Na₂SO₄ and then it was filtered with a glass funnel and a small cotton ball. The solvent was removed under vacuum. Yield = 65 %.

First scaling up procedure (1L-reactor):

A 1L three-necked round bottom flask, equipped with a temperature probe, a constant flow oxygen inlet consisting of a fritted glass tube dipped in the solution, and a gas outlet, was charged with Mn(OAc)₃ • 2H₂O (6.125 mmol, 1.73 g), Mn(OAc)₂ • 4H₂O (6.125 mmol, 1.58 g) and glacial acetic acid (8.5 mol, 490 mL) under an argon flow (0.3 L/min). The mixture was stirred for about 20 minutes at 35 °C with a magnetic stir bar to promote the catalysts dissolution. Then, under argon flow, the reagents were added in the following order: 2-butyl-1-hexene (**2**) (0.245 mol, 37.35 g), methyl acetoacetate (**1**) (0.245 mol, 26.7 mL). The mixture was stirred for 10 minutes at 35 °C. A constant flow of oxygen (0.1 L/min) was introduced into the mixture by a fritted glass tube. The reaction was stirred for 3 hours at 35 °C. The product formation was monitored by TLC after one and two hours from the oxygen addition. After 3 hours, the flask was placed in an ice bath and the acidic mixture was slowly quenched with NaOH (10 M) until neutral pH. The solution was extracted with AcOEt (3 x 200 mL) and the organic phase was washed with NaHCO₃ (saturated solution, 3 x 200 mL). The organic phase was dried on Na₂SO₄ and then it was filtered with a glass funnel and a small cotton ball. The solvent was removed under reduced pressure leaving a white solid material corresponding to product **7** (45.6 g, 60 % yield).

Second scaling up procedure (3L-reactor):

A 3L three-necked cylindrical flask was charged with Mn(OAc)₃ • 2H₂O (12.5 mmol, 3.53 g), Mn(OAc)₂ • 4H₂O (12.5 mmol, 3.22 g) and glacial acetic acid (20 mol, 1155 mL) under argon flow (0.3 L/min). The mixture was stirred for about 20 minutes at 35 °C with a mechanical stirrer connected to an impeller pitched-blade helix to promote the catalysts dissolution. Then, under argon flow, the reagents were added in the following order: 2-butyl-1-hexene

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>)

When citing, please refer to the published version.

(**2**) (0.5 mol, 70 g), methyl acetoacetate (**1**) (0.5 mol, 54.5 mL). The mixture was stirred for 10 minutes at 35 °C. To monitor temperature during the reaction, a temperature probe was fitted into one of the five reactor necks. A constant flow of oxygen (0.1 L/min) was introduced into the mixture using a sintered glass candle. The reaction was stirred for 3 hours at 35 °C. The product formation was monitored by TLC after one and two hours from the oxygen addition. After 3 hours the reaction was quenched with NaOH (10 M), using a Julabo F25 circulator cooling system connected to the reactor jacket (coolant mixture water/ethylene glycol in ratio 1:1 V/V, 0 °C), until neutral pH. The solution was extracted with AcOEt (3 x 500 mL) and the organic phase was washed with NaHCO₃ (saturated solution, 3 x 500 mL). The organic phase was dried on Na₂SO₄ and then it was filtered with a glass funnel and a cotton ball. The solvent was removed under vacuum leaving a white solid material corresponding to product **7** (77.7 g, 50 % yield).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at...

Additional details on reaction quenching, solvent screening (LRA model), statistical analysis (DoE results), purification system, additional details with photographs on 1 L and 3 L reaction set-up, calorimetric studies, spectra of synthesized compounds **2** and **7**.

AUTHOR INFORMATION

Corresponding Authors

Roger Marti – Institut ChemTech, HES-SO, Hochschule für Technik und Architektur, Boulevard de Pérolles 80, CH-1700 Freiburg, Switzerland; orcid.org/0000-0001-6308-4908; Email: Roger.Marti@hefr.ch

Arianna Quintavalla – Alma Mater Studiorum, University of Bologna, Department of Chemistry “G. Ciamician”, Via Selmi 2, 40126 Bologna, Italy; orcid.org/0000-0002-0993-6855; Email: arianna.quintavalla@unibo.it.

Authors

Davide Lardani – Institut ChemTech, HES-SO, Hochschule für Technik und Architektur, Boulevard de Pérolles 80, CH-1700 Freiburg, Switzerland; orcid.org/0000-0001-5733-013X. Email: davide.lardani@unifr.ch.

Marco Lombardo – Alma Mater Studiorum, University of Bologna, Department of Chemistry “G. Ciamician”, Via Selmi 2, 40126 Bologna, Italy; orcid.org/0000-0001-8415-8363. E-mail: marco.lombardo@unibo.it.

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>)

When citing, please refer to the published version.

Claudio Trombini – Alma Mater Studiorum, University of Bologna, Department of Chemistry “G. Ciamician”, Via Selmi 2, 40126 Bologna, Italy; orcid.org/0000-0003-4600-9150. E-mail: claudio.trombini@unibo.it.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

D.L. thanks the Institut ChemTech, HES-SO, Hochschule für Technik und Architektur of Freiburg for hosting him as a student of the University of Bologna with a six months Erasmus fellowship. This research was also supported by the University of Bologna (RFO) and Fondazione CarisBo (project 18668 “Tecnologie avanzate per il controllo e lo sviluppo di molecole innovative per la salute”).

REFERENCES

-
- ⁱ Musser, M. T. Cyclohexanol and cyclohexanone. In *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH, 2005, DOI: 10.1002/14356007.a08_217.
- ⁱⁱ Nowacka, A.; Briantais, P.; Prestipino, C.; Llabrés I.; Xamena, F. X. Selective aerobic oxidation of cumene to cumene hydroperoxide over mono- and bimetallic trimesate metal–organic frameworks prepared by a facile “green” aqueous synthesis. *ACS Sust. Chem. Eng.* **2019**, *7*, 7708–7715.
- ⁱⁱⁱ Cavani, F.; Teles, J. H. Sustainability in catalytic oxidation: an alternative approach or a structural evolution? *ChemSusChem* **2009**, *2*, 508–534.
- ^{iv} Fernandes, R. A.; Jha, A. K.; Kumar, P. Recent advances in Wacker oxidation: from conventional to modern variants and applications. *Catal. Sci. Technol.* **2020**, *10*, 7448–7470.
- ^v Tomás, R. A. F.; Bordado, J. C. M.; Gomes, J. F. P. p-Xylene oxidation to terephthalic acid: a literature review oriented toward process optimization and development. *Chem. Rev.* **2013**, *113*, 7421–7469.
- ^{vi} Mallat, T.; Baiker, A. Oxidation of Alcohols with Molecular Oxygen on Solid Catalysts. *Chem. Rev.* **2004**, *104*, 3037–3058.
- ^{vii} Venart, J. E. S. Flixborough: the explosion and its aftermath. *Process Saf. Environ. Prot.* **2004**, *82*(B2), 105–127.
- ^{viii} Andraos, J. *Synthesis Green Metrics*, CRC Press, 2019.

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>)

When citing, please refer to the published version.

Andraos, J. Application of Green Metrics Analysis to Chemical Reactions and Synthesis Plans. In *Green Chemistry Metrics: Measuring and Monitoring Sustainable Processes*; Lapkin, A., David, J. C., Eds.; Wiley: 2008; pp 69-199.

^x Trost, B. M. The Atom Economy—A Search for Synthetic Efficiency. *Science* **1991**, *254*, 1471-1477.

^{xi} Trost, B. M. Atom Economy—A Challenge for Organic Synthesis: Homogeneous Catalysis Leads the Way. *Angew. Chem. Int. Ed.* **1995**, *34*, 259-281.

^{xii} Campbell, A. N.; Stahl, S. S. Overcoming the “Oxidant Problem”: Strategies to Use O₂ as the Oxidant in Organometallic C-H Oxidation Reactions Catalyzed by Pd (and Cu). *Acc. Chem. Res.* **2012**, *45*, 851-863.

^{xiii} Pierson, D. A.; Olsen, B. A.; Robbins, D. K.; DeVries, K. M.; Varie, D. L. Approaches to Assessment, Testing Decisions, and Analytical Determination of Genotoxic Impurities in Drug Substances. *Org. Proc. Res. Develop.* **2009**, *13*, 285-291.

^{xiv} *ICH Harmonisation for Better Health, Quality Guidelines*.

<http://ich.org/page/quality-guidelines/> (accessed 2021-09-15).

^{xv} Persico, M.; Quintavalla, A.; Rondinelli, F.; Trombini, C.; Lombardo, M.; Fattorusso, C.; Azzarito, V.; Taramelli, D.; Parapini, S.; Corbett, Y.; Chianese, G.; Fattorusso, E.; Taglialatela-Scafati, O. A new class of antimalarial dioxanes obtained through a simple two-step synthetic approach: rational design and structure–activity relationship studies. *J. Med. Chem.* **2011**, *54*, 8526–8540.

^{xvi} Ubale, A. S.; Chaudhari, M. B.; Shaikh, M. A.; Gnanaprakasam, B. Manganese-catalyzed synthesis of quaternary peroxides: application in catalytic deperoxidation and rearrangement reactions. *J. Org. Chem.* **2020**, *85*, 10488–10503.

^{xvii} Vil', V. A.; dos Passos Gomes, G.; Bityukov, O. V.; Lyssenko, K. A.; Nikishin, G. I.; Alabugin, I. V.; Terent'ev, A. O. Interrupted Baeyer–Villiger rearrangement: building a stereoelectronic trap for the Criegee intermediate. *Angew. Chem. Int. Ed.* **2018**, *57*, 3372–3376.

^{xviii} Wang, L.; Ma, Y.; Jiang, Y.; Lv, L.; Li, Z. A Mn-catalyzed remote C(sp³)–H bond peroxidation triggered by radical trifluoromethylation of unactivated alkenes. *Chem. Commun.* **2021**, *57*, 7846–7849.

^{xix} Huang, Z.; Guan, R.; Shanmugam, M.; Bennett, E. L.; Robertson, C. M.; Brookfield, A.; McInnes, E. J. L.; Xiao, J. Oxidative cleavage of alkenes by O₂ with a non-heme manganese catalyst. *J. Am. Chem. Soc.* **2021**, *143*, 10005–10013.

^{xx} Tategami, S-i.; Yamada, T.; Nishino, H.; Korp, J. D.; Kurosawa, K. Formation of 1,2-dioxacyclohexanes by the reaction of alkenes with tris(2,4-pentadionato) manganese(III) or with β-ketocarbonyl compounds in the presence of manganese(III) acetate. *Tetrahedron Lett.* **1990**, *31*, 6371–6374.

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>)

When citing, please refer to the published version.

^{xxi} Yamada, T.; Iwahara, Y.; Nishino, H.; Kurosawa, K. Manganese-(II) and (III)-mediated free-radical cyclisation of alkenes, β -Keto Esters and Molecular Oxygen. *J. Chem. Soc. Perkin 1* **1993**, 609–616.

^{xxii} For the role of manganese(II) in the reaction system see: Nishino, H. Manganese(III)-based peroxidation of alkenes to heterocycles. *Top. Heterocycl. Chem.* **2006**, 6, 39–76, and references therein.

^{xxiii} WWO, *World Malaria Report*. 2020.

<https://www.who.int/publications/i/item/9789240015791>(accessed 2021-09-15).

^{xxiv} WWO, *Leishmaniasis*. 2020. <https://www.who.int/news-room/fact-sheets/detail/leishmaniasis> (accessed 2021-09-15).

^{xxv} Lobo, L.; Cabral, L. I.; Sena, M. I.; Guerreiro, B.; Rodrigues, A. S.; de Andrade-Neto, V. F.; Cristiano, M. L. S.; Nogueira, F. New endoperoxides highly active in vivo and in vitro against artemisinin-resistant *Plasmodium falciparum*. *Malaria J.* **2018**, 17, 145.

^{xxvi} Tiwari, M. K.; Chaudhary, S. Artemisinin-derived antimalarial endoperoxides from bench-side to bed-side: Chronological advancements and future challenges. *Med. Res. Rev.* **2020**, 40, 1220-1275.

^{xxvii} Loo, C. S. N.; Lam, N. S. K.; Yu, D.; Su, X.-z.; Lu, F. Artemisinin and its derivatives in treating protozoan infections beyond malaria. *Pharmacol. Res.* **2017**, 117, 192–217.

^{xxviii} Persico, M.; Parapini, S.; Chianese, G.; Fattorusso, C.; Lombardo, M.; Petrizza, L.; Quintavalla, A.; Rondinelli, F.; Basilico, N.; Taramelli, D.; Trombini, C.; Fattorusso, E.; Taglialatela-Scafati, O. Further optimization of plakortin pharmacophore: structurally simple 4-oxymethyl-1,2-dioxanes with promising antimalarial activity. *Eur. J. Med. Chem.* **2013**, 70, 875–886.

^{xxix} Lombardo, M.; Sonawane, D. P.; Quintavalla, A.; Trombini, C.; Dhavale, D. D.; Taramelli, D.; Corbett, Y.; Rondinelli, F.; Fattorusso, C.; Persico, M.; Taglialatela-Scafati, O. Optimized synthesis and antimalarial activity of 1,2-dioxane-4-carboxamides. *Eur. J. Org. Chem.* **2014**, 1607–1614.

^{xxx} Sonawane, D. P.; Persico, M.; Corbett, Y.; Chianese, G.; Di Dato, A.; Fattorusso, C.; Taglialatela-Scafati, O.; Taramelli, D.; Trombini, C.; Dhavale, D. D.; Quintavalla, A.; Lombardo, M. New antimalarial 3-methoxy-1,2-dioxanes: optimization of cellular pharmacokinetics and pharmacodynamics properties by incorporation of amino and N-heterocyclic moieties at C4. *RSC Adv.* **2015**, 5, 72995–73010.

^{xxxi} Sonawane, D. P.; Corbett, Y.; Dhavale, D. D.; Taramelli, D.; Trombini, C.; Quintavalla, A.; Lombardo, M. D-glucose-derived 1,2,4-trioxepanes: synthesis, conformational study, and antimalarial activity. *Org. Lett.* **2015**, 17, 4074–4077.

^{xxxii} Persico, M.; Fattorusso, R.; Taglialatela-Scafati, O.; Chianese, G.; de Paola, I.; Zaccaro, Z.; Rondinelli, F.; Lombardo, M.; Quintavalla, A.; Trombini, C.; Fattorusso, E.; Fattorusso, C.; Farina, B. The interaction of heme with plakortin and a synthetic

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>)

When citing, please refer to the published version.

endoperoxide analogue: new insights into the heme-activated antimalarial mechanism. *Sci. Rep.* **2017**, *7*, 45485.

^{xxxiii} Ortalli, M.; Varani, S.; Rosso, C.; Quintavalla, A.; Lombardo, M.; Trombini, C. Evaluation of synthetic substituted 1,2-dioxanes as novel agents against human leishmaniasis. *Eur. J. Med. Chem.* **2019**, *170*, 126–140.

^{xxxiv} Ortalli, M.; Varani, S.; Cimato, G.; Veronesi, R.; Quintavalla, A.; Lombardo, M.; Monari, M.; Trombini, C. Evaluation of the Pharmacophoric Role of the O-O Bond in Synthetic Antileishmanial Compounds: Comparison between 1,2-Dioxanes and Tetrahydropyrans. *J. Med. Chem.* **2020**, *63*, 13140–13158.

^{xxxv} National Research Council (NRC), *Prudent Practices in the Laboratory Handling and Management of Chemical Hazards*, the National Academies Press, 2011, pp 65-74. <https://sols.asu.edu/sites/default/files/safety/Prudent%20Practices%20in%20the%20Lab%202011.pdf> (accessed 2021-09-15).

^{xxxvi} Peer, M. Performing Hazardous Reactions with Sodium Azide. *Spec. Chem.* **1998**, *18*, 256–263.

^{xxxvii} Devoille, A.; Uerdingen, M. Safe Processes and high purity for a high-tech market. *Spec. Chem.* **2013**, 18–20.

^{xxxviii} Sperry, J. B.; Azuma, M.; Stone, S. Explosive Hazard Identification in Pharmaceutical Process Development: A Novel Screening Method and Workflow for Shipping Potentially Explosive Materials. *Org. Process Res. Dev.* **2021**, *25*, 212–224.

^{xxxix} dos Passos Gomes, G.; Vil', V.; Terent'ev, A.; Alabugin, I. V. Stereoelectronic source of the anomalous stability of bis-peroxides. *Chem. Sci.* **2015**, *6*, 6783-6791.

^{xl} Gemoets, H. P. L.; Su, Y.; Shang, M.; Hessel, V.; Luque, R.; Noël, T. Liquid phase oxidation chemistry in continuous-flow microreactors. *Chem. Soc. Rev.* **2016**, *45*, 83-117.

^{xli} When air is used as the oxidant, for many chemicals the lower explosion limit (LEL) and the upper explosion limit (UEL) are known. They express the explosive concentration range of the chemical in air.

^{xlii} Osterberg, P. M.; Niemeier, J. K.; Welch, C. J.; Hawkins, J. M.; Martinelli, J. R.; Johnson, T. E.; Root, T. W.; Stahl, S. S. Experimental Limiting Oxygen Concentrations for Nine Organic Solvents at Temperatures and Pressures Relevant to Aerobic Oxidations in the Pharmaceutical Industry. *Org. Process Res. Dev.* **2015**, *19*, 1537–1543.

^{xliii} Mondal, M.; Bora, U. Recent advances in manganese(III) acetate mediated organic synthesis. *RSC Adv.* **2013**, *3*, 18716–18754.

- ^{xliv} Wu, X.; Deng, Z.; Yan, J.; Zhang, Z.; Zhang, F.; Zhang, Z. Experimental investigation on the solubility of oxygen in toluene and acetic acid. *Ind. Eng. Chem. Res.* **2014**, *53*, 9932–9937.
- ^{xlv} Mallia, C. J.; Baxendale, I. R. The Use of Gases in Flow Synthesis. *Org. Process Res. Dev.* **2016**, *20*, 327–360.
- ^{xlvi} Dietrich, N.; Hebrard, G. Visualisation of gas-liquid mass transfer around a rising bubble in a quiescent liquid using an oxygen sensitive dye. *Heat and Mass Transfer* **2018**, *54*, 2163–2171.
- ^{xlvii} On the basis of enthalpy of vaporization values at standard conditions, [acetic acid (51.6 kJ/mol), 2-butyl-1-hexene (37.3 kJ/mol) and methyl acetoacetate (45.4 kJ/mol)], 2-butyl-1-hexene is supposed to be the most easily strippable component of the reaction mixture in the oxygen stream.
- ^{xlviii} Terent'ev, A. O.; Borisov, D. A.; Vil', V. A.; Dembitsky, V. M. Synthesis of five- and six-membered cyclic organic peroxides: Key transformations into peroxide ring-retaining products. *Beilstein J. Org. Chem.* **2014**, *10*, 34–114.
- ^{xlix} Kumabe, R.; Nishino, H. A unique peroxide formation based on the Mn(III)-catalyzed aerobic oxidation. *Tetrahedron Lett.* **2004**, *45*, 703–706.
- ⁱ Li, P.; Zhao, J.; Xia, C.; Li, F. Direct Oxidative Coupling of Enamides and 1,3-Dicarbonyl Compounds: A Facile and Versatile Approach to Dihydrofurans, Furans, Pyrroles, and Dicarbonyl Enamides. *Org. Lett.* **2014**, *16*, 5992–5995.
- ⁱⁱ Snider, B. B.; McCarthy, B. A. Ligand, Solvent, and Deuterium Isotope Effects in Mn(III)-Based Oxidative Free-Radical Cyclizations. *J. Org. Chem.* **1993**, *58*, 6217–6223.
- ⁱⁱⁱ Nishino, H. The facile synthesis of dihydrofurans by the oxidation of olefins with tris(2,4-pentanedionato)manganese(III). *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1922–1927.
- ^{liii} Chuang, C.-P.; Chen, Y.-J. Manganese(III) acetate mediated oxidative radical cyclizations of α -substituted N-[2-(phenylethynyl)phenyl]acetamides. *Tetrahedron* **2016**, *72*, 1911–1918.
- ^{liv} Sato, T.; Hamada, Y.; Sumikawa, M.; Araki, S.; Yamamoto, H. Solubility of Oxygen in Organic Solvents and Calculation of the Hansen Solubility Parameters of Oxygen. *Ind. Eng. Chem. Res.* **2014**, *53*, 19331–19337.
- ^{lv} Ramesh, H.; Mayr, T.; Hobisch, M.; Borisov, S.; Klimant, I.; Krühne, U.; Woodley, J. M. Measurement of oxygen transfer from air into organic solvents. *J. Chem. Technol. Biotechnol.* **2016**, *91*, 832–836.
- ^{lvi} Tseng, C.-M.; Wu, Y.-L.; Chuang, C.-P. Solvent effects on the oxidative free radical reactions of 2-amino-1,4-naphthoquinones. *Tetrahedron* **2004**, *60*, 12249–12260.
- ^{lvii} Matsumoto, R.; Nishino, H. Advanced synthesis of dihydrofurans: effect of formic acid on the Mn(III)-based oxidation. *Synth. Commun.* **2015**, *45*, 1807–1816.

- ^{lviii} Asahi, K.; Nishino, H. Synthesis of bicyclo[3.1.0]hexan-2-ones by manganese(III) oxidation in ethanol. *Synthesis* **2009**, 3, 409-423.
- ^{lix} Räisänen, M. T.; Al-Hunaiti, A.; Atosuo, E.; Kemell, M.; Leskelä, M.; Repo, T. Mn(II) acetate: an efficient and versatile oxidation catalyst for alcohols *Catal. Sci. Technol.* **2014**, 4, 2564–2573.
- ^{lx} Dias, A. M. A.; Bonifácio, R. P.; Marrucho, I. M.; Pádua, A. A. H.; Costa Gomes, M. F. Solubility of oxygen in *n*-hexane and in *n*-perfluorohexane. Experimental determination and prediction by molecular simulation. *Phys. Chem. Chem. Phys.*, **2003**, 5, 543–549.
- ^{lxi} Dias, A. M. A.; Gonçalves, C. M. B.; Legido, J. L.; Coutinho, J. A. P.; Marrucho, I. M. Solubility of oxygen in substituted perfluorocarbons. *Fluid Phase Equilibria* **2005**, 238, 7–12.
- ^{lxii} Sánchez, M. A.; Mainar, A. M.; Pardo, J. I.; López, M. C.; Urieta, J. S. Solubility of nonpolar gases in 2,2,2-trifluoroethanol and 1,1,1,3,3,3-hexafluoropropan-2-ol at several temperatures and 101.33 kPa partial pressure of gas. *Can. J. Chem.* **2001**, 79, 1460–1465.
- ^{lxiii} American Chemical Society, Committee on Chemical Safety, Task Force for Safety Education Guidelines. *Identifying and Evaluating Hazards in Research Laboratories*. American Chemical Society, 2015. <https://www.acs.org/content/dam/acsorg/about/governance/committees/chemical-safety/publications/identifying-and-evaluating-hazards-in-research-laboratories.pdf> (accessed 2021-09-15).
- ^{lxiv} Burnett, L. C. Risk Assessment in the Research Laboratory. *Curr. Protoc. Essent. Lab. Tech.* **2017**, 15, A.1B.1–A.1B.11.
- ^{lxv} Baybutt, P. A critique of the Hazard and Operability (HAZOP) study. *J. Loss Prev. Process Ind.* **2015**, 33, 52-58.
- ^{lxvi} Choi, J.-Y.; Byeon, S.-H. HAZOP Methodology Based on the Health, Safety, and Environment Engineering. *Int. J. Environ. Res. Public Health* **2020**, 17, 3236.
- ^{lxvii} Dunjón, J.; Fthenakis, V.; Vélchez, J. A.; Arnaldos, J. Hazard and operability (HAZOP) analysis. A literature review. *Journal of Hazardous Materials* **2010**, 173, 19–32.
- ^{lxviii} Montgomery, D. C. *Design and Analysis of Experiments*, 10th ed.; Wiley, 2017.
- ^{lxix} Lee, R. Statistical Design of Experiments for Screening and Optimization. *Chem. Ing. Tech.* **2019**, 91, 3, 191–200.

- ^{lxx} Antony, J.; Viles, E.; Fonseca Torres, A.; Incerti de Paula, T.; Machado Fernandes, M.; Cudney, E. A. Design of experiments in the service industry: a critical literature review and future research directions. *Total Qual. Manag.* **2020**, *32*, 1159-1175.
- ^{lxxi} Snider, B. B. Manganese(III)-Based Oxidative Free-Radical Cyclizations. *Chem. Rev.* **1996**, *96*, 339-363.
- ^{lxxii} Ceyhan, S.; Cetinkaya, Y.; Akdag, A.; Balci, M. Regioselectivity observed in manganese(III) acetate mediated addition of acetylacetone to various alkenes: mechanistic and theoretical studies. *Tetrahedron* **2016**, *72*, 6815-6824.
- ^{lxxiii} Yuan, W.; Wei, Y.; Shi, M. Manganese(III)-mediated oxidative annulation of vinylidenecyclopropanes with 1,3-dicarbonyl compounds. *Tetrahedron* **2011**, *67*, 7139-7142.
- ^{lxxiv} Huynh, T-T.; Yamakawa, H.; Nguyen, V-H.; Nishino, H. Mn(III)-Based Oxidative Cyclization of Alkenes Using Tricarbonyl System. *ChemistrySelect* **2018**, *3*, 6414-6420.
- ^{lxxv} Aslan, H.; Öktemer, A.; Dal, H.; Hökelek, T. Synthesis of ferrocene substituted dihydrofuran derivatives via manganese(III) acetate mediated radical addition-cyclization reactions. *Tetrahedron* **2017**, *73*, 7223-7232.
- ^{lxxvi} Andraos, J. Unification of Reaction Metrics for Green Chemistry: Applications to Reaction Analysis. *Org. Process Res. Dev.* **2005**, *9*, 149-163.
- ^{lxxvii} Linde GmbH. *Inerting in the chemical industry*. https://www.boconline.co.uk/en/images/Inerting-in-the-chemical-industry_tcm410-166975.pdf (accessed 2021-09-15).
- ^{lxxviii} Peelen, R. V.; Ramakers, B. P.; Koopmans, A. The dangers of argon, an inert industrial gas: beware of asphyxiation. *Neth. J. Crit. Care* **2019**, *27*, 165-168.
- ^{lxxix} Hub, L.; Suter, G.W.; Schwaninger, M. «Adiabatic» Temperature Rise in Systems with Gas Release, *Chem. Eng. Trans.* **2019**, *77*, 343-348.
- ^{lxxx} Malow, M.; Wehrstedt, K. D. Prediction of the self-accelerating decomposition temperature (SADT) for liquid organic peroxides from differential scanning calorimetry (DSC) measurements. *J. Hazard. Mat.* **2005**, *A120*, 21-24.
- ^{lxxxi} Barontini F., Landucci G., Bimbi M., Graziano G., Nicoletta C. Thermal hazard analysis of organic peroxides by adiabatic calorimetry. *Chem. Eng. Trans.* **2017**, *57*, 415-420.
- ^{lxxxii} Duh, Y-S.; Yo, J-M.; Lee, W-L.; Kao, C-S.; Hsu, J-M. Thermal decompositions of dialkyl peroxides studied by DSC. *J. Therm. Anal. Calorim.* **2014**, *118*, 339-347.

-
- ^{lxxxiii} Tsai, L-C.; Chen, J-W.; Hou, H-Y.; Liu, S-H.; Shu, C-M. Exothermic behaviors in decomposition of three solid organic peroxides by DSC and VSP2. *J. Therm. Anal. Calorim.* **2012**, *109*, 1303–1309.
- ^{lxxxiv} Wu, S-H.; Shyu, M-L.; I, Yet-Pole.; Chi, J-H.; Shu, C-M. Evaluation of runaway reaction for dicumyl peroxide in a batch reactor by DSC and VSP2. *J. Loss Prev. Process Ind.* **2009**, *22*, 721–727.
- ^{lxxxv} Atheaya, H.; Khan, S. I.; Mamgain, R.; Rawat, D. S. Synthesis, thermal stability, antimalarial activity of symmetrically and asymmetrically substituted tetraoxanes. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1446–1449.
- ^{lxxxvi} Jones, A. B.; Wang, J.; Hamme A. T.; Han, W. Oxygen. In: *Encyclopedia of reagents for organic synthesis*. Wiley 2013, DOI: 10.1002/04708 4289x .ro028 .pub3.
- ^{lxxxvii} Hone, C. A.; Roberge, D. M.; Kappe, C. O. The Use of Molecular Oxygen in Pharmaceutical Manufacturing: Is Flow the Way to Go? *ChemSusChem* **2016**, *9*, 1–11.
- ^{lxxxviii} Hone, C. A.; Kappe, C. O. The use of molecular oxygen for liquid phase aerobic oxidations in continuous flow. *Top. Curr. Chem.* **2019**, DOI: 10.1007/s41061-018-0226-z.