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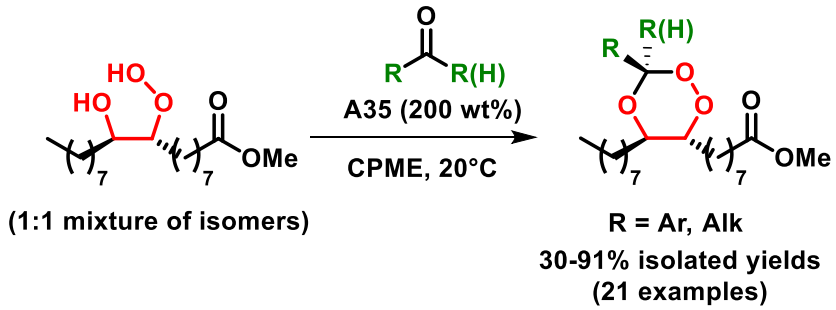


(1:1 mixture of isomers)

R = Ar, Alk
30-91% isolated yields
(21 examples)

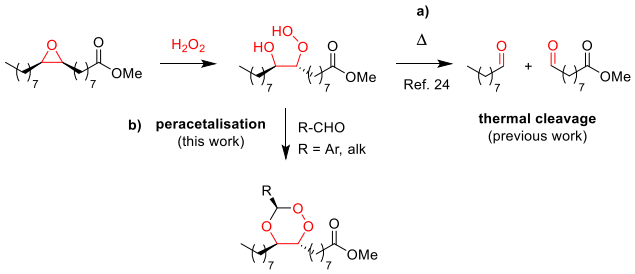
Abstract The peracetalisation of a β-hydroxy hydroperoxide derived from methyl oleate was studied using benzaldehyde as a model substrate to give the corresponding fatty 1,2,4-trioxane. The desired product was obtained as a mixture of regioisomers but only one diastereoisomer of each was formed. The nature of the acid catalyst was studied and both *para*-toluene sulfonic acid (PTSA) and Amberlyst A35 (A35) were found to be efficient homogeneous and heterogeneous catalysts, respectively. The nature of the solvent was also investigated and ethereal solvents such as 2-methyltetrahydrofuran (2-MeTHF), methyl *tert*-butyl ether (MTBE) and cyclopentyl methyl ether (CPME) gave the best NMR yield (85%) for the preparation of the fatty trioxane. The optimized conditions were applied to a range of aromatic and aliphatic aldehydes and the corresponding 1,2,4-trioxanes were isolated with 30-91% yields (21 examples). The antimalarial activity of 3 trioxanes was studied against Plasmodium falciparum, however, no significant activity was detected (IC_{50} > 1600 nM).

Key words β-Hydroxy hydroperoxides; Aldehydes; Peracetalisation; 1,2,4-Trioxanes, Fatty acids.

Organic peroxides and hydroperoxides are encountered in numerous natural products and biologically-active compounds, and also as reaction intermediates.[1] Among organic peroxides, 1,2,4-trioxanes have attracted a lot of attention in medicinal chemistry as they were found to exhibit a wide range of biological activities such as anti-fungal,[2] anti-tumor,[3] anti-tuberculous,[4] amongst others.[5] Nevertheless, the interest of 1,2,4-trioxanes is mainly driven by the fact that this motif is present in artemisinin (Qinghaosu) and its derivatives, that are exhibiting excellent antimalarial activities.[6]

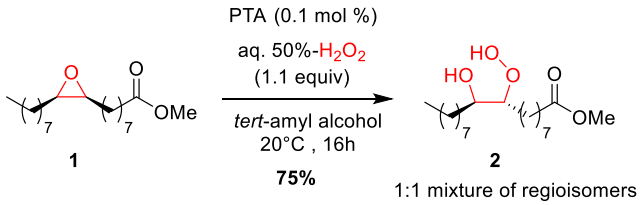
From a synthetic point of view, the 1,2,4-trioxane core can be formed by reaction of endoperoxides with carbonyl compounds.[7] Moreover, it can also be obtained by photooxygenation of several substrates such as β-ionone derivatives,[8] enol ethers[9] and dihydropyrans.[10] However, the peracetalisation of β-hydroxy hydroperoxides with aldehydes and ketones probably offers the most straightforward access.[11] Indeed, β-hydroxy hydroperoxides are readily accessible starting materials considering that they can be efficiently produce by photooxygenation of allylic alcohols[12] or by ring-opening of epoxides with H_2O_2.[13] The peracetalization of β-hydroxy hydroperoxides was first reported by Payne and Smith in 1957.[14] Then, several Brönsted acids were reported to promote the reaction such as *para*-toluenesulfonic acid (PTSA)[15] and camphorsulfonic acid (CSA).[15a,b] Such conditions were successfully implemented in the synthesis of artemisinin.[16] The reaction can be also catalysed by Lewis acids such as BF_3.[17] Recently, the group of Zhang reported that $FeCl_3/SiO_2$ can be used as an efficient supported Lewis acid.[18] Other systems such as copper(II) sulfate,[19] pyridinium *para*-toluene sulfonate (PPTS)[20] and silica sulphuric acid (SSA)[21] were also reported. Despite the interest of 1,2,4-trioxanes, only a limited number of catalysts were reported so far for the peracetalization of β-HHP. Moreover, the reported yields are usually unoptimized considering that the targeted trioxanes are prepared in small quantities in order to evaluate their antimalarial activities. So, the main challenge is to find suitable catalysts and reaction conditions that could allow the preparation of the desired products with high yields, while limiting the formation of byproducts such as diols and carbonyl compounds, produced by reduction and acid-catalysed cleavage of β-HHP, respectively. However, to the best of our knowledge, no such systematic study has been reported so far, especially on fatty acid derivatives.

We are involved for several years in a research programme aiming at the valorisation of vegetable oil derivatives,[22] including using organocatalysis.[23] In this context, we have recently reported that biobased aldehydes can be produced from fatty epoxides through the thermal cleavage of β-hydroxy hydroperoxides.[24] We now report the preparation of fatty 1,2,4-trioxanes by peracetalisation of fatty β-hydroxy hydroperoxides with a range of aldehydes and ketones (Scheme 1).



Scheme 1. Cleavage of fatty β-hydroxy hydroperoxide to carbonyl compounds (a) and peracetalisation to 1,2,4-trioxanes (b).

The β-hydroxy hydroperoxide derived from methyl oleate was selected as a model substrate for the optimization of the reaction conditions. It was prepared by ring-opening of the corresponding epoxide **1** with H_2O_2 (50 wt% aqueous solution) in the presence of phosphotungstic acid (PTA, 0.1 mol%) in *tert*-amyl alcohol. Under these conditions, the desired compound **2** (1:1 mixture of regioisomers) was obtained with 75% isolated yield, on a 5-g scale (Scheme 2).

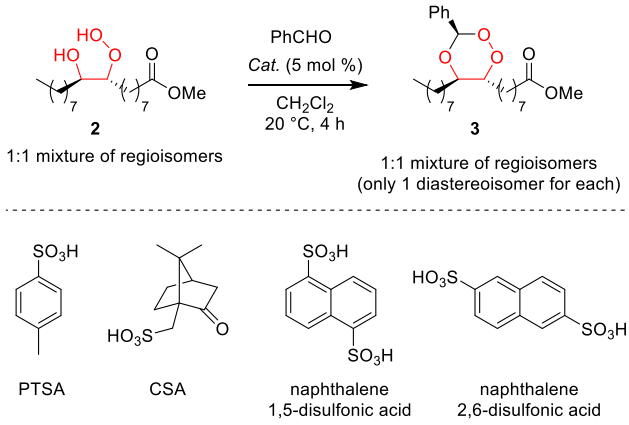


Scheme 2. Preparation of fatty β-hydroxy hydroperoxide **2**.

The reaction conditions were studied using **2** and benzaldehyde as model substrates. The influence of the nature of the acid catalyst was first probed using homogeneous catalysts (5 mol%) (Table 1). The reaction was performed in CH_2Cl_2 at room temperature for 4 hours. Using $BF_3.Et_2O$ as a Lewis acid, the conversion of **2** was complete and trioxane **3** was obtained with 74% yield as determined by ^1H NMR on the crude reaction mixture (Table 1, entry 1). The use of Brönsted acids such as *para*-toluene sulfonic acid (PTSA), camphorsulfunic acid (CSA) and methanesulfonic acid gave similar results with about 74-75% yield of **3** (Table 1, entries 2-4). However, trifluoromethanesulfonic acid only gave 63% yield under the same conditions (Table 1, entry 5). Interestingly, disulfonic acids such as naphthalene-1,5-disulfonic acid (Armstrong's acid) and its isomer naphthalene-2,6-disulfonic acid, also proved to be suitable for this transformation (Table 1, entries 6-7). Acidic resins were next considered with a catalyst loading of 10 wt%. Amberlysts such as A15, A35 and A36 were tested and gave incomplete conversions. Among those heterogeneous catalysts, A35 gave the best result with 41% yield of **3** (Table 1, entries 8-10). Other acidic resins such a Nafion and Aquivion gave poor conversions and yields (Table 1, entries 11-12). Dowex 50 was used as an ion-exchange resin but, despite a relatively good selectivity, gave only 6 % yield (Table 1, entry 13). Finally, a control reaction was also carried out without catalyst. Under these conditions, the desired product **3** was still formed but as traces (Table 1, entry 14). This result indicates that the peracetalisation could be self-catalyzed by the β-hydroxy hydroperoxide **2**, due to the relatively high acidity of the hydroperoxy proton.

From these results, we selected PTSA as the best homogeneous acid, notably for cost and availability reasons. Moreover, we have also selected A35 as a heterogeneous catalyst for further studies in order to simplify the reaction work-up.

Table 1. Screening of acid catalysts.[a]

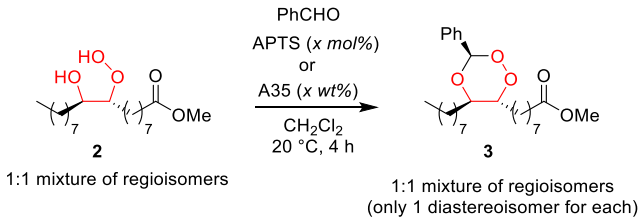


Entry	Catalyst	Conv.[b] **2** (%)	Yield[c] **3** (%)
1	$BF_3.Et_2O$	99	74
2	PTSA	99	75
3	CSA	99	75
4	CH_3SO_3H	99	74
5	CF_3SO_3H	99	63
6	naphthalene-1,5-disulfonic acid	99	73
7	naphthalene-2,6-disulfonic acid	94	75
8	A15	70	39
9	A35	76	41
10	A36	20	29
11	Nafion	23	1
12	Aquivion	20	7
13	Dowex 50	8	6
14	none	1	traces

[a] Reaction conditions: fatty β-hydroxy hydroperoxide **2** (100 mg, 0.29 mmol), benzaldehyde (0.29 mmol, 1 equiv), acid catalyst (5 mol%) or acidic resins (10 wt%), CH_2Cl_2 (3 mL), rt, 4 hours. [b] Conversion of **2** was determined by HPLC. [c] Yield of **3** was determined by ^1H NMR by integration of the signal at 6.2 ppm (characteristic of fatty 1,2,4-trioxane **3**) and integration of the signal at 0.87 ppm (characteristic of the CH_3 end chain present in all species).

Consequently, the influence of the catalyst loading was studied using PTSA and A35 for the peracetalisation of **2** with benzaldehyde (Table 2). With PTSA, the conversion was complete even using only 1 mol% and **3** was obtained with 73% yield (Table 2, entry 1). Progressively increasing the catalyst loading from 1 to 10 mol% increases the yield of **3** from 73 to 78% (Table 1, entries 1-4). However, this improvement was not really significant considering that 10 times more catalyst was used. On the contrary, with A35, both the conversion of **2** and yield of **3** improved when increasing the catalyst loading from 10 to 200 wt% (Table 2, entries 5-9). Satisfyingly, a 81% yield of the desired trioxane **3** can be achieved using 200 wt% of A35. Note that this yield could not be improved by adding benzaldehyde in excess (Table 2, entry 10).

Table 2. Influence of catalyst loading.[a]



2
1:1 mixture of regioisomers

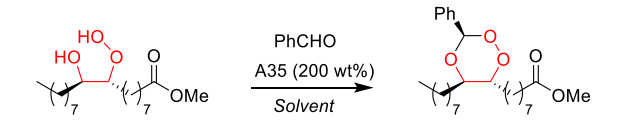
3
1:1 mixture of regioisomers
(only 1 diastereoisomer for each)

Entry	Catalyst	Cat. Loading (%)	Conv.[b] **2** (%)	Yield[c] **3** (%)
1	PTSA	1	99	73
2		2.5	99	76
3		5	99	77
4		10	99	78
5	A35	10	76	41
6		20	80	46
7		50	99	65
8		100	99	71
9		200	99	81
10[d]		200	99	75

[a] Reaction conditions: fatty β-hydroxy hydroperoxide **2** (100 mg, 0.29 mmol), benzaldehyde (0.29 mmol, 1 equiv), PTSA (1-10 mol%) or A35 (10-200 wt%), CH_2Cl_2 (3 mL), rt, 4 hours. [b] Conversion of **2** was determined by HPLC. [c] Yield of **3** was determined by ^{1}H NMR by integration of the signal at 6.2 ppm (characteristic of fatty 1,2,4-trioxane **3**) and integration of the signal at 0.87 ppm (characteristic of the CH_3 end chain present in all species).

Dichloromethane was initially used for the optimization of the reaction parameters as it is traditionally the solvent of choice for performing peracetalisation reactions. However, it is a chlorinated solvent that is currently suspected to be mutagenic, reprotoxic and carcinogenic (MRC), so its replacement by another solvent is highly desirable. Consequently, several solvents were next screened for the model reaction catalysed by A35 (Table 3). The screening of alcohols was first investigated (Table 3, entries 1-4). At first, it could be counter-intuitive to select alcohols for performing peracetalisation reactions as they could form acetals with benzaldehyde, especially in the presence of methanol or ethanol. However, the formation of such species is not deleterious for the reaction outcome as 1,2,4-trioxanes could be potentially produced by transacetalisation of dialkyl acetals. Methanol and ethanol gave comparable results (73-74% yield) but slightly lower than DCM (Table 3, entries 1-2). *Tert*-butanol and *tert*-amyl alcohol gave poor results, probably due to the low solubility of the starting material in these solvents (Table 3, entries 2-4). Dimethyl carbonate was also tested but only gave 54 % yield of the desired trioxane (Table 3, entry 5). Then, ethereal solvents were screened. The use of bio-based 1,2,3-trimethoxypropane (1,2,3-TMP), obtained by permethylation of glycerol,[25] only produces the desired trioxane with 52% yield (Table 3, entry 6). Tetrahydrofuran (THF) and 2-methyltetrahydrofuran (2-MeTHF) proved to be better candidates and gave much better results with 82 and 85% yield, respectively (Table 3, entries 7-8). Similarly, the use of methyl *tert*-butyl ether (MTBE) and cyclopentyl methyl ether (CPME) also allows forming fatty trioxane **3** with high yields (Table 3, entries 9-10).

Table 3. Screening of solvents.[a]



2
1:1 mixture of regioisomers

3
1:1 mixture of regioisomers
(only 1 diastereoisomer for each)

Entry	Solvent	Conv.[b] **2** (%)	Yield[c] **3** (%)
1	MeOH	99	73
2	EtOH	99	74
3	*tert*-BuOH	85	65
4	*tert*-amyl alcohol	88	10
5	DMC	78	54
6	1,2,3-TMP	99	52
7	THF	99	82
8	2-MeTHF	99	85
9	MTBE	99	84
10	CPME	99	85

[a] Reaction conditions: fatty β-hydroxy hydroperoxide **2** (100 mg, 0.29 mmol), benzaldehyde (0.29 mmol, 1 equiv), A35 (200 wt%), solvent (3 mL), rt, 4 hours. [b] Conversion of **2** was determined by HPLC. [c] Yield of **3** was determined by ^{1}H NMR by integration of the signal at 6.2 ppm (characteristic of fatty 1,2,4-trioxane **3**) and integration of the signal at 0.87 ppm (characteristic of the CH_3 end chain present in all species). DMC: dimethyl carbonate, 1,2,3-TMP: 1,2,3-trimethoxypropane, THF: tetrahydrofuran, 2-MeTHF: 2-methyltetrahydrofuran, MTBE: methyl *tert*-butyl ether, CPME: cyclopentyl methyl ether.

From these results, CPME was selected to study the scope of the reaction. Indeed, this solvent gave the best results and was found more general than 2-MeTHF and MTBE throughout the scope. The scope of the reaction was then investigated under the optimized conditions [A35 (200 wt%), CPME, 20°C, 4 hours] using β-hydroxy hydroperoxide **2** and a range of aromatic aldehydes (Figure 1).

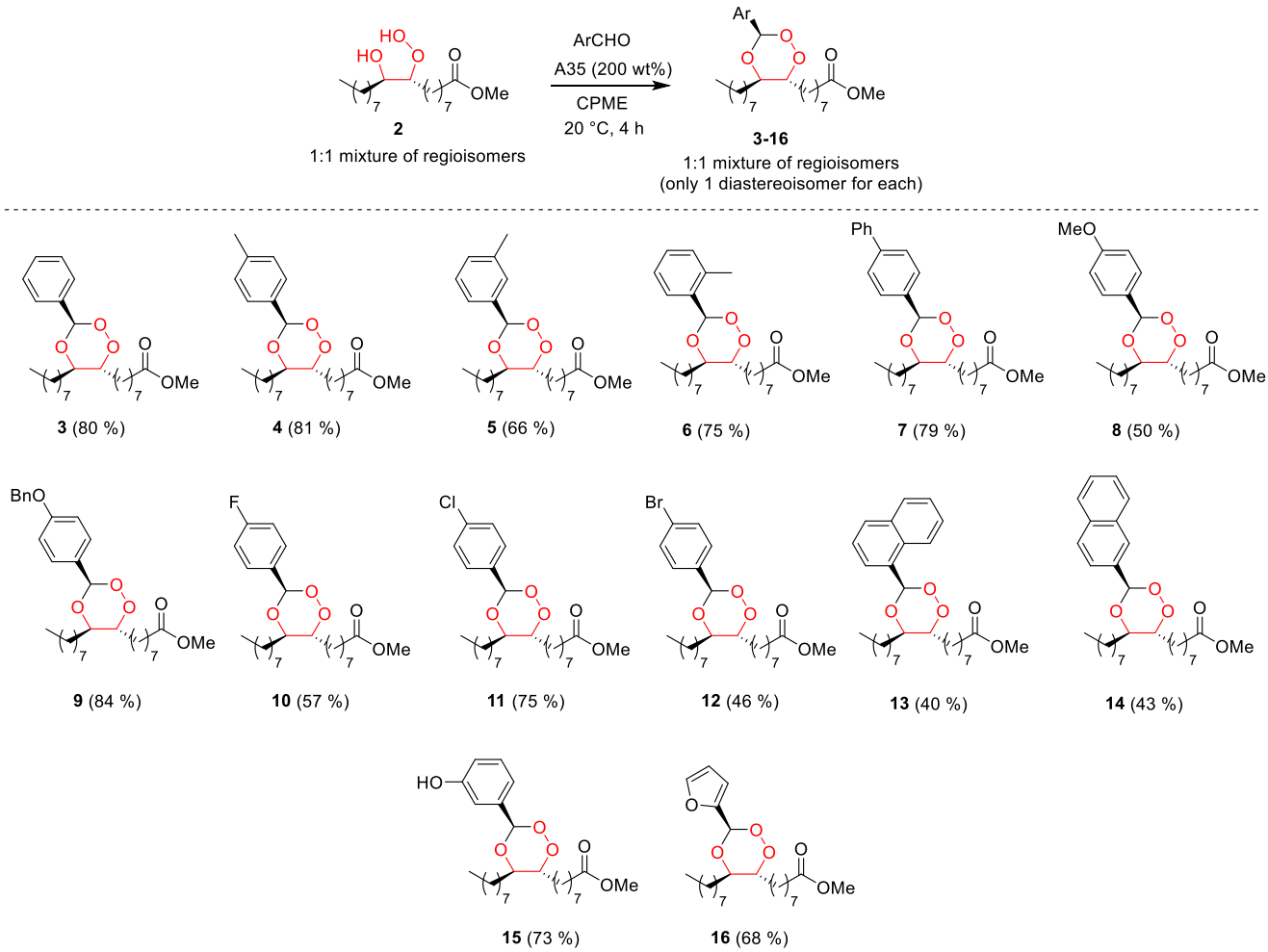


Figure 1. Preparation of 1,2,4-trioxanes from β-hydroxy hydroperoxide **2** and a range of aromatic aldehydes.

Repeating the reaction with benzaldehyde gave the desired trioxane **3** with 80% isolated yield after purification by column chromatography. With *para*-, *meta*- and *ortho*-tolualdehydes, trioxanes **4-6** were isolated with 66-81% yield. Other aldehydes bearing a *para*- substituent such as Ph, OMe and OBn were also tested and gave trioxanes **7-9** with 50-84% yield. The presence of halogen (Br, Cl, F) was also well tolerated, giving the desired products **10-12** with 46-75% yield. When using 1- and 2-naphthaldehyde, trioxanes **13-14** were isolated with moderate 40 and 43% yield, respectively. The reaction also tolerates the presence of a free hydroxyl group, considering that compound **15**, prepared from 3-hydroxybenzaldehyde, was obtained with 73% yield. Finally, the use of furfural gave **16** with 68% yield.

The reaction scope was next investigated with a range of aliphatic aldehydes and ketones (Figure 2). Paraformaldehyde was first used but no reaction took place, probably due to the fact that it did not depolymerised to formaldehyde under our mild reaction conditions. So, other linear aldehydes such as acetaldehyde, butanal, nonanal were also tested and the corresponding compounds **17-19** were isolated with 46-91% yield. It is worth noting that **19** can be considered as a 100%-biobased product as nonanal can be produced by oxidative cleavage of vegetable oil derivatives.[23a-b,24] The use of branched aldehydes such as isobutyraldehyde and pivalaldehyde gave trioxanes **20-21** with 50 and 34% yield, respectively. This shows that the steric hindrance is deleterious for the peracetalization process. Ketones such as acetone and cyclohexanone were also tested and the desired products **22-23** were obtained with moderate yields (30-51%). Noteworthy, acetophenone was tested as an aryl alkyl ketone but no reaction occurs under the optimized conditions. Consequently, 2,2,2-trifluoroacetophenone was also used as an activated ketone but only traces of the desired trioxane were detected by ^{1}H and ^{19}F NMR.

Overall, the use of A35 as a catalyst for the peracetalisation of β-hydroxy hydroperoxides with aldehydes and ketones allowed the preparation of a range of 1,2,4-trioxanes with moderate to high yields. Moreover, the use of such acidic resin has considerably simplified the workup since it can be easily removed from the reaction mixture by filtration. Finally, the

recycling of Amberlyst A35 was also studied with benzaldehyde over 3 consecutive runs. After each reaction, the resin was filtered and reused as such for the next run. Under these conditions, the yield of **3** progressively decreased from 81% (first run) to 49% (second run), then to 25% (third run). However, the catalytic activity can be partially restored to 45% (fourth run) after treatment of the resin with aqueous 1M HCl.

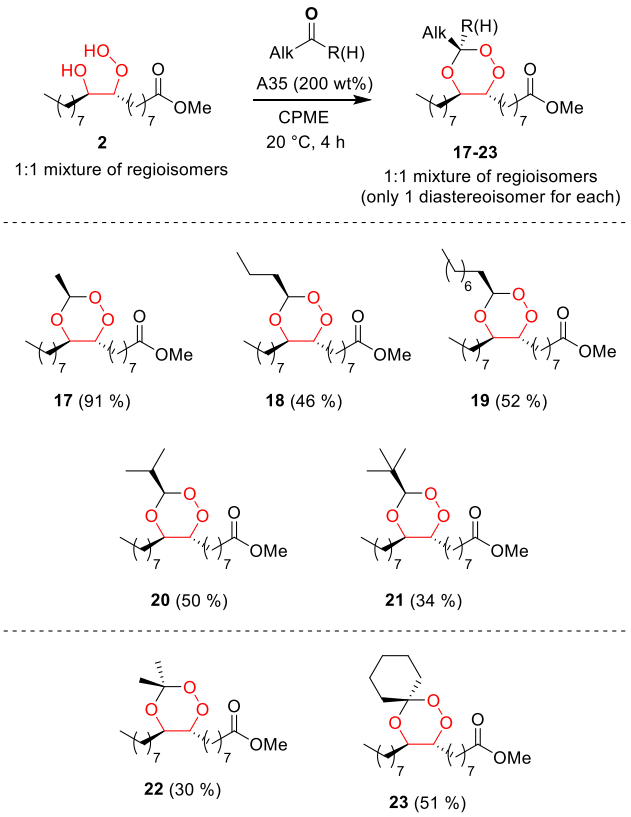


Figure 2. Preparation of 1,2,4-trioxanes from β-hydroxy hydroperoxide **2** and a range of aliphatic aldehydes and ketones.

The primary objective of this work was to develop a convenient method for the peracetalisation of β-hydroxy hydroperoxides, notably targeting fatty 1,2,4-trioxanes. However, considering that 1,2,4-trioxanes could present some antimalarial activities, it became evident that such new species should be tested for such activities. One chloroquine-sensitive (3D7) and one chloroquine-resistant (W2) clones of *Plasmodium falciparum* were tested for *in vitro* susceptibility to chloroquine compared to trioxanes **3**, **22** and **23** but also to β-hydroxy hydroperoxides **2**. First, used as controls, the IC50 of chloroquine against sensitive clone 3D7 (21.7 ± 0.65 nM) and resistant clone W2 (508 ± 13.2 nM) were similar to the expected values. However, none of the tested compounds provided a significant decrease in parasite growth and their IC50 were estimated > 1600 nM which was the highest tested concentration. These results were attributed to the poor solubility of the fatty compounds. Consequently, no further test was performed with the other compounds.

In conclusion, we have reported the first synthesis of fatty 1,2,4-trioxanes by peracetalization of β-hydroxy hydroperoxides with a range of aldehydes and ketones. Several sulfonic acids were found suitable to catalyze such transformation and Amberlyst A35 was selected as a heterogeneous catalyst for further studies. We also found that ethereal solvents such as 2-MeTHF, MTBE and CMPE can be efficiently used as CH_2Cl_2 alternatives. The optimized conditions were applied to a range of aldehydes and ketones and the corresponding fatty 1,2,4-trioxanes were obtained with 30-91% isolated yields (21 examples). Some compounds were tested as antimalarial agents but none of them exhibit interesting activities.

Experimental section

All solvents were commercially available and used without any further purification. Reactions were monitored by TLC using aluminium silica gel (60F254). They were carried out on a plate of 0.20 mm silica gel. For revelations, UV (λ = 254 nm) light was provided (Universal UV lamp CAMAC). A phosphomolybdic acid solution or KMnO4 solution was used to reveal the TLC plate if necessary. Purification by flash chromatography was performed using silica gel 60H (40-63µ). Nuclear magnetic resonance spectra were recorded on a Brüker DRX 300, Brüker ALS 300 (^{1}H: 300 MHz, ^{13}C: 75 MHz), Brüker ADVANCEIII 500, Brüker BBO probe, Brüker BBI probe (^{1}H: 500 MHz, ^{13}C: 125 MHz). Chemical shifts are given with reference to residual DMSO or $CHCl_3$ central peaks: 2.50 and 7.26 ppm for proton, 39.52 and 77.16 ppm for carbon, respectively. J values are given in Hertz (Hz). Abbreviations are defined as follows: s = singlet, d = doublet, dd = doublet of doublet, ddd = doublet of doublet of doublet, t = triplet, q = quadruplet, qt = quintet, hex = hexuplet, hept = heptuplet, m = multiplet.

Preparation of methyl 9(10)-hydroperoxy-10(9)-hydroxyoctadecanoate (2): In a dry glass reactor, methyl 8-(3-octyloxiran-2-yl)octanoate (5.26 g, 16.8 mmol) was dissolved in *tert*-amyl alcohol (60 mL) and phosphotungstic acid (PTA, 0.1 mol%) was added. Then, H_2O_2 (50 wt% in water) (1 mL, 35 mmol) was added dropwise. The flask was closed under argon atmosphere and magnetically stirred at 20°C for 16 hours. After the reaction completion was confirmed by TLC (Cyclohexane/Ethyl acetate – 60/40), 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. The product was purified by column chromatography (cyclohexane/ethyl acetate – 60/40) to give (2) (4.43 g, 75%) as a colorless oil.

^{1}H NMR (300 MHz, *d*6-DMSO, 1:1 mixture of regioisomers) δ_H = 11.22 (s, 1H), 4.38 (d, *J* = 5.3 Hz, 1H), 3.68 – 3.60 (m, 2H), 3.57 (s, 3H), 2.28 (t, *J* = 7.4 Hz, 2H), 1.60-1.10 (m, 26H), 0.85 (t, *J* = 6.6 Hz, 3H).

^{13}C NMR (75 MHz, d_6-DMSO, 1:1 mixture of regioisomers) δc = 173.37 ($C{=}O_{ester}$), 87.38 (C-OOH), 69.21 (C-OH), 51.17 (OCH_3), 33.29 (CH_2), 31.34 (CH_2), 31.07 (CH_2), 29.29 (CH_2), 29.12 (CH_2), 28.99 (CH_2), 28.77 (CH_2), 28.66 (CH_2), 28.47 (CH_2), 26.82 (CH_2), 25.89 (CH_2), 25.82 (CH_2), 24.47 (CH_2), 22.15 (CH_2), 13.99 (CH_3).

HRMS (ESI$^+$): *m/z* $[M+Na]^+$ calcd for $C_{19}H_{38}NaO_5$: 369.2611, found: 369.2619.

General procedure for the preparation of fatty 1,2,4-trioxanes

Methyl 9(10)-hydroperoxy-10(9)-hydroxyoctadecanoate (172 mg, 0.5 mmol), aldehyde (0.5 mmol), Amberlyst™ 35 DRY (344 mg, 200 wt%) and cyclopentyl methyl ether (5 mL) were added in a dry glass reactor. The mixture was stirred at room temperature for 4 to 16 hours. After the reaction completion was confirmed by TLC (Pentane/diethyl ether – 95/5), Amberlyst™ 35 DRY was removed through vacuum filtration. The solvent was removed under reduced pressure to give the crude product. Crude fatty 1,2,4-trioxanes were purified by flash chromatography column (40g of silica / mmol) with a mixture of pentane and diethyl ether as eluent to give pure product.

Methyl 8-(5-octyl-3-phenyl-1,2,4-trioxan-6-yl)octanoate (3). The title compound was synthesized from benzaldehyde (61 mg, 0.58 mmol) by following the general procedure. The product was purified by column chromatography (pentane/diethylether – 95/5) to give (3) (200 mg, 80%) as a colorless oil.

^{1}H NMR (300 MHz, d_6–DMSO, 1:1 mixture of regioisomers): δ_H = 7.73 – 7.19 (m, 5H), 6.16 (s, 1H), 4.07 (td, *J* = 8.4, 4.9 Hz, 1H), 3.69 (td, *J* = 8.5, 2.7 Hz, 1H), 3.56 (d, *J* = 4.0 Hz, 3H), 2.27 (td, *J* = 7.2, 4.0 Hz, 2H), 1.69 – 1.43 (m, 6H), 1.40 – 1.13 (m, 20H), 0.85 (t, *J* = 5.4 Hz, 3H).

^{13}C NMR (75 MHz, d_6–DMSO, 1:1 mixture of regioisomers): δ_C = 173.32 (CO_{ester}), 134.69 (Cq_{ar}), 129.78 (2 CH_{ar}), 128.33 (2 CH_{ar}), 126.91 (CH_{ar}), 103.28 ($CH_{peracetal}$), 83.17 (CH-OO), 77.94 (CH-O), 51.14 (OCH_3), 33.28 (CH_2), 31.29 (CH_2), 29.82 (CH_2), 28.97 (CH_2), 28.90 (CH_2), 28.77 (CH_2), 28.67 and 28.64 (CH_2), 28.58 (CH_2), 28.43 and 28.38 (CH_2), 28.20 (CH_2), 24.57 and 24.51 (CH_2), 24.42 (CH_2), 24.27 and 24.23 (CH_2), 22.12 (CH_2), 13.94 (CH_3).

HRMS (ESI$^+$): *m/z* $[M+Na]^+$ calcd for $C_{26}H_{42}NaO_5$: 457.2924; found: 457.2930.

Methyl 8-(5-octyl-3-(p-tolyl)-1,2,4-trioxan-6-yl)octanoate (4). The title compound was synthesized from 4-methylbenzaldehyde (60 mg, 0.5 mmol) by following the general procedure. The product was purified by column chromatography (pentane/diethylether – 95/5) to give (4) (181 mg, 81%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$, 1:1 mixture of regioisomers): δ_H = 7.45 – 7.33 (m, 2H), 7.24-7.13 (m, 2H), 6.13 (s, 1H), 4.15 (td, *J* = 8.7, 2.7 Hz, 1H), 3.69 – 3.63 (m, 1H), 3.66 and 3.66 (s, 3H, OCH_3), 2.35 (s, 3H), 2.30 (t, *J* = 7.5 Hz, 2H), 1.70 – 1.48 (m, 7H), 1.43 – 1.19 (m, 19H), 0.88 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$, 1:1 mixture of regioisomers): δ_C =174.35 (CO_{ester}), 139.67 (Cq_{ar}), 132.12 (Cq_{ar}), 129.09 (2 CH_{ar}), 126.94 (2 CH_{ar}), 104.07 ($CH_{peracetal}$), 83.72 and 83.68 (CH-OO), 78.90 and 78.86 (CH-O), 51.54 (OCH_3), 34.17 (CH_2), 31.98 and 31.96 (CH_2), 30.72 and 30.68 (CH_2), 29.78 and 29.73 (CH_2), 29.61 and 29.56 (CH_2), 29.51 and 29.47 (CH_2), 29.39 and 29.32 (CH_2), 29.26 and 29.19 (CH_2), 29.13 (CH_2), 29.08 and 29.03 (CH_2), 25.22 and 25.15 (CH_2), 25.01 (CH_2), 24.94 and 24.88 (CH_2), 22.78 (CH_2), 21.45 (CH_3), 14.22 (CH_3).

HRMS (ESI$^+$): *m/z* $[M+Na]^+$ calcd for $C_{27}H_{44}NaO_5$: 471.3081; found: 471.3078.

Methyl 8-(5-octyl-3-(m-tolyl)-1,2,4-trioxan-6-yl)octanoate (5). The title compound was synthesized from 3-methylbenzaldehyde (60 mg, 0.5 mmol) by following the general procedure. The product was purified by column chromatography (pentane/diethylether – 95/5) to give (5)(148 mg, 66%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$, 1:1 mixture of regioisomers): δ_H = 7.33 – 7.22 (m, 3H), 7.21 – 7.15 (m, 1H), 6.13 (s, 1H), 4.16 (td, *J* = 8.7, 2.7 Hz, 1H), 3.70 – 3.63 (m, 1H), 3.66 and 3.66 (s, 3H, OCH_3), 2.36 (s, 3H), 2.30 (t, *J* = 7.5 Hz, 2H), 1.68 – 1.46 (m, 8H), 1.40 – 1.18 (m, 18H), 0.88 (t, *J* = 6.7 Hz 3H).

^{13}C NMR (75 MHz, $CDCl_3$, 1:1 mixture of regioisomers): δ_C = 174.36 (CO_{ester}), 138.14 (Cq_{ar}), 134.85 (Cq_{ar}), 130.53 (CH_{ar}), 128.35 (CH_{ar}), 127.56 (CH_{ar}), 124.13 (CH_{ar}), 104.16 ($CH_{peracetal}$), 83.79 and 83.76 (CH-OO), 78.97 and 78.94 (CH-O), 51.55 (OCH_3), 34.18 (CH_2), 31.99 and 31.97 (CH_2), 30.71 and 30.68 (CH_2), 29.78 and 29.72 (CH_2), 29.61 and 29.57 (CH_2), 29.50 and 29.48 (CH_2), 29.40 and 29.33 (CH_2), 29.27 and 29.21 (CH_2), 29.14 (CH_2), 29.07 and 29.02 (CH_2), 25.22 and 25.15 (CH_2), 25.02 (CH_2), 24.97 and 24.93 (CH_2), 22.79 (CH_2), 21.50 (CH_3), 14.22 (CH_3).

HRMS (ESI$^+$): *m/z* $[M+Na]^+$ calcd for $C_{27}H_{44}NaO_5$: 471.3081; found: 471.3071.

Methyl 8-(5-octyl-3-(o-tolyl)-1,2,4-trioxan-6-yl)octanoate (6). The title compound was synthesized from 2-methylbenzaldehyde (60 mg, 0.5 mmol) by following the general procedure. The product was purified by column chromatography (pentane/diethylether – 95/5) to give (6)(168 mg, 75%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, 1:1 mixture of regioisomers): δ_H = 7.50 (dt, *J* = 7.4, 1.7 Hz, 1H), 7.21 – 7.05 (m, 3H), 6.21 (s, 1H), 4.10 (td, *J* = 8.9, 2.6 Hz, 1H), 3.63 – 3.57 (m, 1H), 3.58 and 3.57 (s, 3H, OCH_3), 2.35 (s, 3H), 2.22 (td, *J* = 7.5, 1.7 Hz, 2H), 1.61 – 1.43 (m, 6H), 1.34 – 1.14 (m, 20H), 0.81 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, 1:1 mixture of regioisomers): δ_C = 174.35 (CO_{ester}), 136.88 (Cq_{ar}), 132.85 (Cq_{ar}), 130.49 (CH_{ar}), 129.61 (CH_{ar}), 126.93 (CH_{ar}), 125.94 (CH_{ar}), 102.35 ($CH_{peracetal}$), 83.73 and 83.70 (CH-OO), 79.01 and 78.98 (CH-O), 51.54 (OCH_3), 34.16 (CH_2), 31.97 and 31.96 (CH_2), 30.70 and 30.67 (CH_2), 29.76 and 29.73 (CH_2), 29.59 and 29.55 (CH_2), 29.50 and 29.47 (CH_2), 29.38 and 29.32 (CH_2), 29.25 and 29.18 (CH_2), 29.12 (CH_2), 29.06 (CH_2), 25.25 and 25.17 (CH_2), 25.00 (CH_2), 24.92 and 24.87 (CH_2), 22.77 (CH_2), 19.05 (CH_3), 14.21 (CH_3).

HRMS (ESI$^+$): *m/z* $[M+Na]^+$ calcd for $C_{27}H_{44}NaO_5$: 471.3081; found: 471.3083.

Methyl 8-(3-([1,1'-biphenyl]-4-yl)-5-octyl-1,2,4-trioxan-6-yl)octanoate (7). The title compound was synthesized from biphenyl-4-carboxaldehyde (91 mg, 0.5 mmol) by following the general procedure. The product was purified by column chromatography (pentane/diethylether – 95/5) to give (7)(201 mg, 79%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$, 1:1 mixture of regioisomers): δ_H = 7.66 – 7.52 (m, 6H), 7.50 – 7.41 (m, 2H), 7.41 – 7.30 (m, 1H), 6.22 (s, 1H), 4.20 (td, *J* = 8.7, 2.6 Hz, 1H), 3.78 – 3.66 (m, 1H), 3.68 and 3.67 (s, 3H), 2.31 (t, *J* = 7.5 Hz, 2H), 1.73 – 1.45 (m, 8H), 1.43 – 1.24 (m, 18H), 0.95 – 0.84 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$, 1:1 mixture of regioisomers): δ_C = 174.36 (CO_{ester}), 142.70 (Cq_{ar}), 140.79 (Cq_{ar}), 133.87 (Cq_{ar}), 128.91 (2 CH_{ar}), 127.65 (CH_{ar}), 127.45 (2 CH_{ar}), 127.33 (2 CH_{ar}), 127.24 (2 CH_{ar}), 103.87 ($CH_{peracetal}$), 83.84 and 83.81 (CH-OO), 78.98 and 78.95 (CH-O), 51.56 (OCH_3), 34.19 (CH_2), 32.00 and 31.97 (CH_2), 30.73 and 30.70 (CH_2), 29.79 and 29.74 (CH_2), 29.63 and 29.58 (CH_2), 29.52 and 29.49 (CH_2), 29.41 and 29.34 (CH_2), 29.28 and 29.21 (CH_2), 29.14 (CH_2), 29.10 and 29.05 (CH_2), 25.23 and 25.16 (CH_2), 25.02 (CH_2), 24.98 and 24.93 (CH_2), 22.79 (CH_2), 14.23 (CH_3).

HRMS (ESI$^+$): *m/z* $[M+Na]^+$ calcd for $C_{32}H_{46}NaO_5$: 533.3237; found: 533.3244.

Methyl 8-(3-(4-methoxyphenyl)-5-octyl-1,2,4-trioxan-6-yl)octanoate (8). The title compound was synthesized from *p*-anisaldehyde (68 mg, 0.5 mmol) by following the general procedure. The product was purified by column chromatography (pentane/diethylether – 95/5) to give (8)(116 mg, 50%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$, 1:1 mixture of regioisomers): δ_H = 7.41 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.10 (s, 1H), 4.14 (td, *J* = 8.8, 2.6 Hz, 1H), 3.78 (s, 3H), 3.67 – 3.62 (m, 1H), 3.65 and 3.64 (s, 3H, OCH_3), 2.29 (t, *J* = 7.5, 2H), 1.67 – 1.49 (m, 6H), 1.50 – 1.21 (m, 20H), 0.87 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$, 1:1 mixture of regioisomers): δ_C = 174.30 (CO_{ester}), 160.67 (Cq_{ar}-OMe), 128.41 (Cq_{ar}), 127.31 (2 CH_{ar}), 113.74 (2 CH_{ar}), 103.86 ($CH_{peracetal}$), 83.58 and 83.55 (CH-OO), 78.88 and 78.85 (CH-O), 55.32 (CH_3-O), 51.50 (OCH_3), 34.12 (CH_2), 31.94 and 31.92 (CH_2), 30.69 and 30.65 (CH_2), 29.75 and 29.68 (CH_2), 29.57 and 29.53 (CH_2), 29.46 and 29.44 (CH_2), 29.35 and 29.29 (CH_2), 29.08 (CH_2), 29.03 (CH_2), 28.98 (CH_2), 25.18 and 25.10 (CH_2), 24.97 and 24.96 (CH_2), 24.90 and 24.84 (CH_2), 22.74 (CH_2), 14.19 (CH_3).

HRMS (ESI$^+$): *m/z* $[M+Na]^+$ calcd for $C_{27}H_{44}NaO_6$: 487.3030; found: 487.3034.

Methyl 8-(3-(4-(benzyloxy)phenyl)-5-octyl-1,2,4-trioxan-6-yl)octanoate (9). The title compound was synthesized from 4-(benzyloxy)benzaldehyde (106 mg, 0.5 mmol) by following the general procedure. The product was purified by column chromatography

(pentane/diethylether – 95/5) to give (9)(227 mg, 84%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$, 1:1 mixture of regioisomers): δ_H = 7.48 – 7.27 (m, 7H), 6.93 – 7.00 (m, 2H), 6.12 (s, 1H), 5.07 (s, 2H), 4.15 (td, *J* = 8.6, 2.6 Hz, 1H), 3.69 – 3.63 (m, 1H), 3.67 and 3.66 (s, 3H, OCH_3), 2.31 (t, *J* = 7.5 Hz, 2H), 1.68 – 1.50 (m, 6H), 1.40 – 1.23 (m, 20H), 0.89 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$, 1:1 mixture of regioisomers): δ_C = 174.36 (CO_{ester}), 159.90 (Cq_{ar}-OMe), 128.70 (2 CH_{ar}), 128.48 (2 CH_{ar}), 128.10 (Cq_{ar}), 127.61 (Cq_{ar}), 127.53 (2 CH_{ar}), 114.76 (2 CH_{ar}), 103.87 ($CH_{peracetal}$), 83.65 and 83.61 (CH-OO), 78.94 and 78.91 (CH-O), 70.09 (CH_2-O), 51.55 (OCH_3), 34.18 (CH_2), 31.98 and 31.97 (CH_2), 30.74 and 30.71 (CH_2), 29.79 and 29.73 (CH_2), 29.61 and 29.58 (CH_2), 29.50 and 29.48 (CH_2), 29.39 and 29.32 (CH_2), 29.26 and 29.20 (CH_2), 29.13 (CH_2), 29.08 and 29.03 (CH_2), 25.22 and 25.15 (CH_2), 25.02 (CH_2), 24.95 and 24.90 (CH_2), 22.78 (CH_2), 14.22 (CH_3).

HRMS (ESI$^+$): *m/z* [M+Na]$^+$ calcd for $C_{33}H_{48}NaO_6$: 563.3343; found: 563.3333.

Methyl 8-(3-(4-fluorophenyl)-5-octyl-1,2,4-trioxan-6-yl)octanoate (10). The title compound was synthesized from 4-fluorobenzaldehyde (62 mg, 0.5 mmol) by following the general procedure. The product was purified by column chromatography (cyclohexane/ethyl acetate – 95/5) to give (10) (129 mg, 57%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$, 1:1 mixture of regioisomers): δ_H = 7.51 – 7.42 (m, 2H), 7.09 – 7.00 (m, 2H), 6.13 (s, 1H), 4.14 (td, *J* = 8.8, 2.7 Hz, 1H), 3.69 – 3.64 (m, 1H), 3.65 and 3.65 (s, 3H, OCH_3), 2.29 (t, *J* = 7.5 Hz, 2H), 1.69 – 1.50 (m, 6H), 1.49 – 1.19 (m, 20H), 0.87 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$, 1:1 mixture of regioisomers): δ_C = 174.35 (CO_{ester}), 163.58 (d, $^1J_{C\text{-}F}$ = 248.3 Hz, Cq_{Ar}), 130.91 (d, $^4J_{C\text{-}F}$ = 3.0 Hz, Cq_{Ar}), 128.99 (d, $^3J_{C\text{-}F}$ = 8.5 Hz, 2 CH_{ar}), 115.40 (d, $^2J_{C\text{-}F}$ = 21.7 Hz, 2 CH_{ar}), 103.30 ($CH_{peracetal}$), 83.77 and 83.74 (CH-OO), 78.99 and 78.96 (CH-O), 51.54 (OCH_3), 34.15 (CH_2), 31.97 and 31.95 (CH_2), 30.67 and 30.64 (CH_2), 29.75 and 29.70 (CH_2), 29.59 and 29.54 (CH_2), 29.47 and 29.46 (CH_2), 29.38 and 29.31 (CH_2), 29.25 and 29.17 (CH_2), 29.11 (CH_2), 29.02 and 28.97 (CH_2), 25.19 and 25.12 (CH_2), 24.99 (CH_2), 24.93 and 24.88 (CH_2), 22.77 (CH_2), 14.21 (CH_3).

^{19}F NMR (272 MHz, $CDCl_3$): δ_F = -111.48 (tt, $^3J_{C\text{-}H}$ = 14.0 Hz, $^4J_{C\text{-}H}$ = 8.7 Hz 1F).

HRMS (ESI$^+$): *m/z* [M+Na]$^+$ calcd for $C_{26}H_{41}NaO_5F$: 475.2830; found: 475.2824.

Methyl 8-(3-(4-chlorophenyl)-5-octyl-1,2,4-trioxan-6-yl)octanoate (11). The title compound was synthesized from 4-chlorobenzaldehyde (70 mg, 0.5 mmol) by following the general procedure. The product was purified by column chromatography (pentane/diethylether – 95/5) to give (11)(176 mg, 75%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$, 1:1 mixture of regioisomers): δ_H = 7.47 – 7.37 (m, 2H), 7.39 – 7.29 (m, 2H), 6.13 (s, 1H), 4.14 (td, *J* = 8.7, 2.7 Hz, 1H), 3.70 – 3.63 (m, 1H), 3.66 and 3.65 (s, 3H, OCH_3), 2.30 (t, *J* = 7.5 Hz, 2H), 1.77 – 1.47 (m, 6H), 1.42 – 1.21 (m, 20H), 0.88 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$, 1:1 mixture of regioisomers): δ_C = 174.35 (CO_{ester}), 135.70 (Cq_{ar}), 133.41 (Cq_{ar}), 128.68 (CH_{ar}), 128.44 (CH_{ar}), 103.22 ($CH_{peracetal}$), 83.87 and 83.84 (CH-OO), 79.01 and 78.98 (CH-O), 51.57 (OCH_3), 34.18 (CH_2), 31.98 and 31.97 (CH_2), 30.67 and 30.64 (CH_2), 29.76 and 29.71 (CH_2), 29.60 and 29.54 (CH_2), 29.49 and 29.47 (CH_2), 29.39 and 29.32 (CH_2), 29.26 and 29.19 (CH_2), 29.13 (CH_2), 29.05 and 29.00 (CH_2), 25.20 and 25.13 (CH_2), 25.01 (CH_2), 24.95 and 24.90 (CH_2), 22.79 (CH_2), 14.22 (CH_3).

HRMS (ESI$^+$): *m/z* [M+Na]$^+$ calcd for $C_{26}H_{41}ClNaO_5$: 491.2535; found: 491.2529.

Methyl 8-(3-(4-bromophenyl)-5-octyl-1,2,4-trioxan-6-yl)octanoate (12). The title compound was synthesized from 4-bromobenzaldehyde (92 mg, 0.5 mmol) by following the general procedure. The product was purified by column chromatography (cyclohexane/ethyl acetate – 95/5) to give (12) (118 mg, 46%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$, 1:1 mixture of regioisomers): δ_H = 7.50 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H), 6.11 (s, 1H), 4.14 (td, *J* = 8.8, 2.7 Hz, 1H), 3.68 – 3.63 (m, 1H), 3.65 and 3.65 (s, 3H, OCH_3), 2.30 (t, *J* = 7.5 Hz, 2H), 1.67 – 1.50 (m, 6H), 1.51 – 1.20 (m, 20H), 0.88 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$, 1:1 mixture of regioisomers): δ_C = 174.36 (CO_{ester}), 133.88 (Cq_{ar}), 131.64 (Cq_{ar}), 128.71 (CH_{ar}), 124.00 (CH_{ar}), 103.25 ($CH_{peracetal}$), 83.87 and 83.85 (CH-OO), 78.99 and 78.97 (CH-O), 51.57 (OCH_3), 34.17 (CH_2), 31.98 and 31.96 (CH_2), 30.66 and 30.63 (CH_2), 29.75 and 29.71 (CH_2), 29.60 and 29.53 (CH_2), 29.48 and 29.47 (CH_2), 29.39 and 29.32 (CH_2), 29.26 and 29.19 (CH_2), 29.12 (CH_2), 29.03 and 28.98 (CH_2), 25.19 and 25.12 (CH_2), 25.01 (CH_2), 24.94 and 24.89 (CH_2), 22.78 (CH_2), 14.23 (CH_3).

HRMS (ESI$^+$): *m/z* [M+Na]$^+$ calcd for $C_{26}H_{41}NaBrO_5$: 535.2030; found: 535.2022.

Methyl 8-(3-(naphthalen-1-yl)-5-octyl-1,2,4-trioxan-6-yl)octanoate (13). The title compound was synthesized from 1-naphthaldehyde (78 mg, 0.5 mmol) by following the general procedure. The product was purified by column chromatography (cyclohexane/ethyl acetate – 95/5) to give (13) (96 mg, 40%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$, 1:1 mixture of regioisomers): δ_H = 7.99 (d, *J* = 1.6 Hz, 1H), 7.90 – 7.81 (m, 3H), 7.59 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.53 – 7.46 (m, 2H), 6.34 (s, 1H), 4.24 (td, *J* = 7.7, 6.5, 1.8 Hz, 1H), 3.75 (dt, *J* = 8.9, 5.4 Hz, 1H), 3.67 and 3.65 (s, 3H, OCH_3), 2.31 (td, *J* = 7.5, 2.7 Hz, 2H), 1.71 – 1.55 (m, 6H), 1.54 – 1.22 (m, 20H), 0.90 (td, *J* = 6.9, 3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$, 1:1 mixture of regioisomers): δ_C = 174.36 (CO_{ester}), 134.06 (Cq_{ar}), 133.00 (Cq_{ar}), 132.29 (Cq_{ar}), 128.58 (CH_{ar}), 128.23 (CH_{ar}), 127.81 (CH_{ar}), 126.79 (CH_{ar}), 126.76 (CH_{ar}), 126.30 (CH_{ar}), 124.21 (CH_{ar}), 104.13 ($CH_{peracetal}$), 83.89 and 83.86 (CH-OO), 79.07 and 79.04 (CH-O), 51.56 and 51.54 (OCH_3), 34.17 (CH_2), 31.98 and 31.97 (CH_2), 30.73 and 30.70 (CH_2), 29.79 and 29.73 (CH_2), 29.62 and 29.57 (CH_2), 29.50 and 29.48 (CH_2), 29.40 and 29.33 (CH_2), 29.27 and 29.20 (CH_2), 29.13 and 29.10 (CH_2), 29.04 (CH_2), 25.23 and 25.16 (CH_2), 25.01 (CH_2), 24.98 (CH_2), 22.78 (CH_2), 14.23 (CH_3).

HRMS (ESI$^+$): *m/z* [M+Na]$^+$ calcd for $C_{30}H_{44}NaO_5$: 507.3081; found: 507.3076.

Methyl 8-(3-(naphthalen-2-yl)-5-octyl-1,2,4-trioxan-6-yl)octanoate (14). The title compound was synthesized from 2-naphtaldehyde (78 mg, 0.5 mmol) by following the general procedure. The product was purified by column chromatography (pentane/diethylether – 95/5) to give (14)(104 mg, 43%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$, 1:1 mixture of regioisomers): δ_H = 8.30 – 8.20 (m, 1H), 7.92 – 7.79 (m, 3H), 7.58 – 7.45 (m, 3H), 6.79 (s, 1H), 4.30 (td, *J* = 8.7, 2.6 Hz, 1H), 3.83 (dt, *J* = 9.1, 5.4 Hz, 1H), 3.67 and 3.65 (s, 3H, OCH_3), 2.32 and 2.30 (t, *J* = 7.5 Hz, 2H), 1.74 – 1.55 (m, 6H), 1.42 – 1.21 (m, 20H), 0.90 (td, *J* = 7.0, 3.7 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$, 1:1 mixture of regioisomers): δ_C = 174.36 (CO_{ester}), 133.71 (Cq_{ar}), 130.90 (Cq_{ar}), 130.38 (CH_{ar})), 130.29 (Cq_{ar}), 128.61 (CH_{ar}), 126.57 (CH_{ar}), 125.87 (CH_{ar}), 125.43 (CH_{ar}), 125.16 (CH_{ar}), 124.07 (CH_{ar}), 102.51 ($CH_{peracetal}$), 83.92 and 83.88 (CH-OO), 79.34 and 79.31 (CH-O), 51.55 and 51.54 (OCH_3), 34.18 (CH_2), 31.98 (CH_2), 30.76

and 30.73 (CH_2), 29.78 and 29.75 (CH_2), 29.61 and 29.56 (CH_2), 29.53 and 29.50 (CH_2), 29.39 and 29.34 (CH_2), 29.26 (CH_2), 29.19 (CH_2), 29.14 (CH_2), 25.28 and 25.20 (CH_2), 25.02 (CH_2), 24.97 and 24.92 (CH_2), 22.78 (CH_2), 14.22 (CH_3).

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{30}H_{44}NaO_5$: 507.3081; found: 507.3070.

Methyl 8-(3-(3-hydroxyphenyl)-5-octyl-1,2,4-trioxan-6-yl)octanoate (15). The title compound was synthesized from 3-hydroxybenzaldehyde (61 mg, 0.5 mmol) by following the general procedure. The product was purified by column chromatography (cyclohexane/ethyl acetate – 95/5) to give (15) (165 mg, 73%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$, 1:1 mixture of regioisomers): δ_H = 7.22 (t, *J* = 8.0 Hz, 1H),7.06 – 6.95 (m, 2H), 6.84 (dtd, *J* = 8.1, 2.6, 1.1 Hz, 1H), 6.12 and 6.10 (s, 1H), 4.15 (tt, *J* = 8.3, 2.5 Hz, 1H), 3.70 – 3.63 (m, 1H), 3.67 and 3.67 (s, 3H, OCH_3), 2.33 and 2.30 (t, *J* = 7.5, Hz, 2H), 1.71 – 1.51 (m, 6H), 1.40 – 1.20 (m, 20H), 0.88 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$, 1:1 mixture of regioisomers): δ_C = 175.14 and 174.76 (CO_{ester}), 155.91 and 155.12 (C_{ar}-OH), 136.39 and 136.32 (Cq_{ar}), 119.25 and 119.15 (CH_{ar}), 129.72 (CH_{ar}), 116.87 (CH_{ar}), 113.91 and 113.67 (CH_{ar}), 103.68 and 103.56 ($CH_{peracetal}$), 83.84 and 83.82 (CH-OO), 78.94 and 78.85 (CH-O), 51.85 and 51.70 (OCH_3), 34.25 and 34.21 (CH_2), 31.98 and 31.96 (CH_2), 30.70 and 30.53 (CH_2), 29.78 and 29.71 (CH_2), 29.61 and 29.47 (CH_2), 29.46 and 29.41 (CH_2), 29.32 and 29.19 (CH_2), 29.10 and 29.09 (CH_2), 29.05 and 28.99 (CH_2), 28.93 and 28.82 (CH_2), 25.20 and 25.12 (CH_2), 24.99 and 24.95 (CH_2), 25.89 and 24.53 (CH_2), 22.77 (CH_2), 14.22 (CH_3).

HRMS (ESI^+): *m/z* $[M+Na]^+$ calcd for $C_{26}H_{42}NaO_6$: 473.2874; found: 473.2879.

Methyl 8-(3-(furan-2-yl)-5-octyl-1,2,4-trioxan-6-yl)octanoate (16). The title compound was synthesized from furfural (48 mg, 0.5 mmol) by following the general procedure. The product was purified by column chromatography (cyclohexane/ethyl acetate – 95/5) to give (16) (144 mg, 68%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$, 1:1 mixture of regioisomers): δ_H = 7.40 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.52 (d, *J* = 3.3 Hz, 1H), 6.36 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.19 (s, 1H), 4.15 (td, *J* = 8.8, 2.7 Hz, 1H), 3.64 and 3.64 (s, 3H, OCH_3), 3.63 – 3.59 (m, 1H), 2.28 and 2.28 (t, *J* = 7.6, Hz, 2H), 1.66 – 1.47 (m, 6H), 1.47 – 1.19 (m, 20H), 0.86 and 0.86 (t, *J* = 6.8, Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$, 1:1 mixture of regioisomers): δ_C = 174.30 (CO_{ester}), 147.93 (Cq_{ar}), 143.32 (CH_{ar}), 110.47 (CH_{ar}), 109.89 (CH_{ar}), 98.68 and 98.67 ($CH_{peracetal}$), 83.85 and 83.82 (CH-OO), 79.37 and 79.33 (CH-O), 51.50 (OCH_3), 34.12 (CH_2), 31.93 and 31.91 (CH_2), 30.57 and 30.53 (CH_2), 29.68 and 29.63 (CH_2), 29.54 (CH_2), 29.46 and 29.41 (CH_2), 29.33 and 29.28 (CH_2), 29.19 and 29.12 (CH_2), 29.07 and 29.06 (CH_2), 28.95 and 28.91 (CH_2), 25.13 and 25.05 (CH_2), 24.96 and 24.92 (CH_2), 24.85 (CH_2), 22.73 (CH_2), 14.18 (CH_3).

HRMS (ESI^+): *m/z* $[M+Na]^+$ calcd for $C_{24}H_{40}NaO_6$: 447.2717; found: 447.2716.

Methyl 8-(3-methyl-5-octyl-1,2,4-trioxan-6-yl)octanoate (17). The title compound was synthesized from Acetaldehyde (22 mg, 0.5 mmol) by following the general procedure. The product was purified by column chromatography (pentane/diethylether – 95/5) to give (17)(170 mg, 91%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$, 1:1 mixture of regioisomers): δ_H = 5.32 (q, *J* = 5.3 Hz, 1H, $CH_{peracetal}$), 3.97 (td, *J* = 8.8, 2.3 Hz, 1H), 3.65 and 3.64 (s, 3H, OCH_3), 3.43 (td, *J* = 8.2, 2.5 Hz, 1H), 2.29 and 2.28 (t, *J* = 7.5, Hz, 2H), 1.69 – 1.54 (m, 2H), 1.54 – 1.38 (m, 5H), 1.37 – 1.15 (m, 22H), 0.91 – 0.83 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$, 1:1 mixture of regioisomers): δ_C = 174.38 and 174.36 (CO_{ester}), 101.61 ($CH_{peracetal}$), 83.54 and 83.51 (CH-OO), 78.43 and 78.40 (CH-O), 51.56 (OCH_3), 34.18 (CH_2), 31.99 and 31.96 (CH_2), 30.68 and 30.64 (CH_2), 29.77 and 29.72 (CH_2), 29.63 and 29.55 (CH_2), 29.50 and 29.46 (CH_2), 29.39 and 29.32 (CH_2), 29.19 (CH_2), 29.28 (CH_2), 28.98 and 28.93 (CH_2), 25.21 and 25.14 (CH_2), 25.01 (CH_2), 25.03 and 24.95 (CH_2), 22.79 and 22.77 (CH_2), 18.10 (CH_3), 14.22 (CH_3).

HRMS (ESI^+): *m/z* $[M+Na]^+$ calcd for $C_{21}H_{40}NaO_5$: 395.2768; found: 395.2769.

Methyl 8-(5-octyl-3-propyl-1,2,4-trioxan-6-yl)octanoate (18). The title compound was synthesized from butyraldehyde (36 mg, 0.5 mmol) by following the general procedure. The product was purified by column chromatography (cyclohexane/ethyl acetate – 95/5) to give (18) (92 mg, 46%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$, 1:1 mixture of regioisomers): δ_H = 5.18 (t, *J* = 5.4 Hz, 1H), 3.96 (td, *J* = 9.0, 2.4 Hz, 1H), 3.65 and 3.64 (s, 3H, OCH_3), 3.41 (td, *J* = 8.6, 2.6 Hz, 1H), 2.29 and 2.27 (t, *J* = 7.5, Hz, 2H), 1.63 – 1.36 (m, 10H), 1.33 – 1.24 (m, 20H), 0.91 (t, *J* = 7.3 Hz, 3H), 0.86 (dt, *J* = 7.1, 3.4 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$, 1:1 mixture of regioisomers): δ_C = 174.38 and 174.36 (CO_{ester}), 104.63 and 104.61 ($CH_{peracetal}$), 83.82 and 83.79 (CH-OO), 78.38 and 78.35 (CH-O), 51.55 (OCH_3), 34.25 (CH_2), 34.18 and 34.17 (CH_2), 31.98 and 31.96 (CH_2), 30.61 and 30.58 (CH_2), 29.70 (CH_2), 29.49 (CH_2), 29.63 and 29.46 (CH_2), 29.38 and 29.31 (CH_2), 29.28 and 29.19 (CH_2), 29.11 (CH_2), 29.03 and 28.98 (CH_2), 25.19 and 25.12 (CH_2), 25.00 (CH_2), 25.02 and 24.94 (CH_2), 22.78 and 22.77 (CH_2), 17.41 (CH_2), 14.22 (CH_3), 14.04 (CH_3).

HRMS (ESI^+): *m/z* $[M+Na]^+$ calcd for $C_{23}H_{44}NaO_5$: 423.3081; found: 423.3076.

Methyl 8-(3,5-dioctyl-1,2,4-trioxan-6-yl)octanoate (19). The title compound was synthesized from Nonanal (71 mg, 0.5 mmol) by following the general procedure. The product was purified by column chromatography (pentane/diethylether – 95/5) to give (19)(123 mg, 52%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$, 1:1 mixture of regioisomers): δ_H = 5.17 (t, *J* = 5.4 Hz, 1H), 3.97 (td, *J* = 8.9, 2.3 Hz, 1H), 3.65 and 3.56 (s, 3H, OCH_3), 3.41 (td, *J* = 8.4, 2.5 Hz, 1H), 2.29 (td, *J* = 7.5, 3.5 Hz, 2H), 1.71 – 1.44 (m, 8H), 1.37 – 1.12 (m, 32H), 0.92 – 0.82 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$, 1:1 mixture of regioisomers): δ_C = 174.37 (CO_{ester}), 104.85 ($CH_{peracetal}$), 83.82 and 83.80 (CH-OO), 78.41 and 78.39 (CH-O), 51.56 (OCH_3), 34.19 (CH_2), 32.26 (CH_2), 32.00 (CH_2), 30.61 (CH_2), 29.72 (CH_2), 29.65 (CH_2), 29.53 (CH_2), 29.50 (2 CH_2), 29.47 and 29.40 (CH_2), 29.32 (CH_2), 29.31 (CH_2), 29.22 (CH_2), 29.13 (CH_2), 29.40 and 28.99 (CH_2), 25.20 and 25.13 (CH_2), 25.02 (CH_2), 25.04 and 24.97 (CH_2), 24.01 (CH_2), 22.80 (CH_2), 22.78 (CH_2), 14.22 (2 CH_3).

HRMS (ESI^+): *m/z* $[M+Na]^+$ calcd for $C_{28}H_{54}NaO_5$: 493.3863; found: 493.3862.

Methyl 8-(3-isopropyl-5-octyl-1,2,4-trioxan-6-yl)octanoate (20). The title compound was synthesized from isobutyraldehyde (36 mg, 0.5 mmol) by following the general procedure. The product was purified by column chromatography (cyclohexane/ethyl acetate – 95/5) to give (20) (100 mg, 50%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$, 1:1 mixture of regioisomers): δ_H = 4.90 (t, *J* = 5.9 Hz, 1H), 3.95 (td, *J* = 9.0, 2.3 Hz, 1H), 3.65 and 3.64 (s, 3H, OCH_3), 3.40 (td, *J* = 8.6, 2.7 Hz, 1H), 2.29 (td, *J* = 7.6, 5.2 Hz, 2H), 1.82 – 1.38 (m, 9H), 1.36 – 1.19 (m, 18H), 0.94 and 0.92 (d, *J* = 5.2 Hz, 6H), 0.87 and 0.86 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$, 1:1 mixture of regioisomers): δ_C = 174.40 and 174.38 (CO_{ester}), 108.08 and 108.06 ($CH_{peracetal}$), 83.85 and 83.82 (CH-OO), 78.34 and 78.31 (CH-O), 51.56 (OCH_3), 34.19 and 34.18 (CH_2), 31.99 and 31.97 (CH_2), 31.25 (CH), 30.56 and 30.53 (CH_2), 29.72 and 29.67 (CH_2), 29.64 and 29.50 (CH_2), 29.47 (CH_2), 29.39 and 29.31 (CH_2), 29.30 and 29.20 (CH_2), 29.12 (CH_2), 29.02 and 28.96 (CH_2), 25.21 and 25.13 (CH_2), 25.03 and 25.01 (CH_2), 24.93 and 24.88 (CH_2), 22.79 and 22.77 (CH_2), 17.23 (2 CH_3), 14.22 (CH_3).

HRMS (ESI^+): *m/z* $[M+Na]^+$ calcd for $C_{23}H_{44}NaO_5$: 423.3081; found: 423.3079.

Methyl 8-(3-(tert-butyl)-5-octyl-1,2,4-trioxan-6-yl)octanoate (21). The title compound was synthesized from pivalaldehyde (43 mg, 0.5 mmol) by following the general procedure. The product was purified by column chromatography (pentane/diethylether – 95/5) to give (21)(70 mg, 34%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$, 1:1 mixture of regioisomers): δ_H = 4.81 (s, 1H), 3.93 (td, *J* = 9.1, 2.3 Hz, 1H), 3.65 and 3.65 (s, 3H, OCH_3), 3.40 (td, *J* = 9.1,

8.6, 2.4 Hz, 1H), 2.29 (td, *J* = 7.5, 4.3 Hz, 2H), 1.67 – 1.54 (m, 2H), 1.53 – 1.38 (m, 4H), 1.38 – 1.17 (m, 20H), 0.92 (s, 9H), 0.90 – 0.80 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$, 1:1 mixture of regioisomers): δ_C = 174.38 (CO_{ester}), 109.40 and 109.38 ($CH_{peracetal}$), 83.78 and 83.75 (CH-OO), 78.28 and 78.26 (CH-O), 51.56 (OCH_3), 34.90 (CH_2), 34.20 and 34.19 (CH_2), 32.00 and 31.97 (CH_2), 30.51 and 30.48 (CH_2), 29 75 (Cq), 29.64 (CH_2), 29.52 and 29.48 (CH_2), 29.44 and 29.38 (CH_2), 29.31 (CH_2), 29.21 and 29.13 (CH_2), 29.02 and 28.96 (CH_2), 25.23 and 25.16 (CH_2), 25.05 and 25.02 (CH_2), 24.91 (3 CH_3), 24.87 and 24.83 (CH_2), 22.80 and 22.78 (CH_2), 14.22 (CH_3).

HRMS (ESI$^+$): *m/z* [M+Na]$^+$ calcd for $C_{24}H_{46}NaO_5$: 437.3227; found: 437.3227.

Methyl 8-(3,3-dimethyl-5-octyl-1,2,4-trioxan-6-yl)octanoate (22). The title compound was synthesized from Acetone (34 mg, 0.58 mmol) by following the general procedure. The product was purified by column chromatography (pentane/diethylether – 95/5) to give (22)(67 mg, 30%) as a colorless oil.

^{1}H NMR (300 MHz, *d*$_6$ - DMSO, 1:1 mixture of regioisomers): δ_H = 3.78 (td, *J* = 10.3, 7.0 Hz, 1H), 3.67 (dt, *J* = 9.4, 4.4 Hz, 1H), 3.57 (s, 3H), 2.28 (t, *J* = 7.4 Hz, 2H), 1.58 – 1.38 (m, 8H), 1.33 – 1.20 (m, 18H), 1.24 (s, 3H), 1.22 (s, 3H), 0.91 – 0.81 (m, 3H).

^{13}C NMR (75 MHz, *d*$_6$-DMSO, 1:1 mixture of regioisomers): δ_C =173.74 (CO_{ester}), 102.57 ($Cq_{peracetal}$), 83.30 (CH-OO), 71.39 (CH-O), 51.58 (OCH_3), 33.71 (CH_2), 31.72 (2 CH_3), 30.63 (CH_2), 29.42 and 29.35 (CH_2), 29.23 (CH_2), 29.24 and 29.23 (CH_2), 29.08 and 29.02 (CH_2), 28.89 and 28.86 (CH_2), 28.83 and 23.70 (CH_2), 26.17 (CH_2), 25.08 and 25.03 (CH_2), 24.85 (CH_2), 24.70 and 24.66 (CH_2), 22.55 (CH_2), 20.78 (CH_2), 14.38 (CH_3).

HRMS (ESI$^+$): *m/z* [M+Na]$^+$ calcd for $C_{22}H_{42}NaO_5$: 409.2924; found: 409.2928.

Methyl 8-(4-octyl-1,2,5-trioxaspiro[5.5]undecan-3-yl)octanoate (23).

The title compound was synthesized from cyclohexanone (57 mg, 0.58 mmol) by following the general procedure. The product was purified by column chromatography (pentane/diethylether – 95/5) to give (23)(108 mg, 51%) as a colorless oil.

^{1}H NMR (300 MHz, *d*$_6$-DMSO, 1:1 mixture of regioisomers): δ_H = 3.84 – 3.74 (m, 1H), 3.70 – 3.60 (m, 1H), 3.57 (s, 3H), 2.28 (t, *J* = 7.4 Hz, 2H), 2.09-2.07 (m, 1H), 1.85-1.83 (m, 1H), 1.61 – 1.37 (m, 12H), 1.32 – 1.18 (m, 22H), 0.85 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (75 MHz, *d*$_6$-DMSO, 1:1 mixture of regioisomers): δ_C = 173.27 (CO_{ester}), 102.07 ($Cq_{peracetal}$), 83.15 (CH-OO), 70.05 (CH-O), 51.10 (OCH_3), 34.52 (CH_2), 33.23 (CH_2), 31.23 and 31.21 (CH_2), 30.07 (CH_2), 28.93 and 28.88 (CH_2), 28.83 (CH_2), 28.75 (CH_2), 28.60 (CH_2), 28.56 (CH_2), 28.41 and 28.38 (CH_2), 28.34 (CH_2), 28.25 (CH_2), 25.05 (CH_2), 24.60 and 24.55 (CH_2), 24.36 (CH_2), 24.32 and 24.28 (CH_2), 22.06 (CH_2), 22.03 (CH_2), 21.86 (CH_2), 13.90 (CH_3).

HRMS (ESI$^+$): *m/z* [M+Na]$^+$ calcd for $C_{25}H_{46}NaO_5$: 449.3252; found: 449.3253.

Procedure for in vitro tests

Chloroquine-sensitive (3D7) and chloroquine-resistant (W2) clones of *Plasmodium falciparum* were provided by the World Wide Antimalarial Resistance Network (WWARN). The clones were cultured in complete RPMI 1640 medium, with 0.5% Albumax + hypoxanthine and gentamicin. They were incubated at 37°C, 5% CO_2, 5% O_2, 90% N_2. An aliquot of the culture was diluted to reduce the parasitaemia to 0.5%, and the haematocrit was adjusted to 1.5%. This suspension was then added (175 µL per well) to microplates predosed with 25 µL of drugs and incubated for 72 hours at 37°, 5% $C0_2$, 5% O_2, 90% N_2. After freeze-thawed process, the test was performed according to the SYBR Green I standard protocol as described.[26] Briefly, after homogenization of the medium, lysis buffer and SYBR Green I were added and fluorescence was read with the fluorimeter Tristar2 (Multimode Reader LB 942 Bertold Technologies) at 485 nm wave length using Microwin 2000 software.

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

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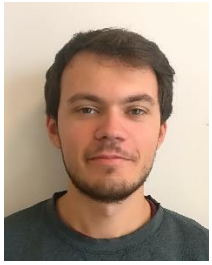
Biosketches

Thomas De Dios Miguel obtained his M.Sc. at the Université de Poitiers, France in 2017. During this time, he carried out two internships. The first one was done in glycochemistry under the guidance of Pr Y. Blériot, and the second one in heterogeneous catalysis under the supervision of Pr K. Vigier. He has done his Ph.D. studies (2018-2021) at the University of Lyon, in the "Institut de Chimie et biochimie Moléculaires & Supramoléculaires" (ICBMS) France, under the supervision of Dr N. Duguet. His Ph.D. project has focused on the valorization of vegetable oil derivatives in continuous flow conditions.

Dan Louvel graduated from the Ecole européenne d'ingénieurs de Chimie, Polymères et Matériaux at the university of Strasbourg, France in 2019. He spent one year in 2018-2019 at the Université du Québec à Montréal, Canada as part of an exchange program. During that period, he joined the group of Pr Sylvain Canesi to develop new synthetic methodology using hypervalent iodine. He went back to France for his M.Sc. internship at the University of Lyon in the "Institut de Chimie et biochimie Moléculaires & Supramoléculaires" (ICBMS) under the guidance of Dr Nicolas Duguet, working on the chemistry of β-hydroxy hydroperoxides. He is now doing his Ph.D. studies in the same institute working with Dr Anis Tlili on the development of photoredox catalysis/small molecules activations, with particular focus on fluorine chemistry.



Killian Onida obtained his master degree at the Université Claude Bernard Lyon 1, France in 2019. During his master studies, he joined the "Institut de Chimie et biochimie Moléculaires & Supramoléculaires" (ICBMS) to carry out two internships. The first one involved palladium-catalyzed C-N bond cleavage under the supervision of Pr A. Amgoune. The second one was dealing about the deoxyfluorination of CO_2 under the supervisation of Dr. A. Tlili. He is currently doing his Ph.D. in the same institute under the supervision of Dr. N. Duguet. His work is focused on the valorisation of carbon dioxide and biomass through the development of original thermomorphic catalysts.

Adeline Lavoignat has been a biology technician since 2007. She obtained her Diploma Advanced Technician in biological and biotechnological analyzes in 2007. She joined the Malaria Research Unit at ICBMS in 2008. She is in charge of Plasmodium falciparum long term in vitro culture and she is performing antimalarial drug resistance tests on a daily basis. She is co-author of 8 articles.

Stephane Picot is Medical Doctor from the University of Grenoble, France since 1989. He received his PhD in 1993 and his Diploma of Medical Mycology from Pasteur Institute in 1995. He graduated from University of Miami, USA in 2006 for Protection of Human Research. He was appointed assistant professor in 1993 at Grenoble University hospital and full professor in 1997 at Lyon University hospital. He was head of the Parasitology and Mycology department at the faculty of medicine and the Hospital of Lyon. He was President of the Consortium Against Parasites & Fungi (2012-2014) and President of Scientific Council of French National Reference Center for Malaria (2016-2020). His current researches are focused on new malaria treatments based on the mechanisms of controlled cell death of *Plasmodium* parasite and on malaria drug resistance. He is conducting clinical trials in malaria endemic areas including Mali, Cameroon and Indonesia.

Nicolas Duguet graduated from Institut National des Sciences Appliquées of Rouen in 2003 and received his Ph.D. in 2006 from the university of Rouen, France (with Dr Jacques Maddaluno). In 2007, he joined the group of Pr Andrew D. Smith at the University of St Andrews, Scotland, UK as a postdoctoral fellow working in the field of organocatalysis. He moved back to France in 2009 for a second postdoc in medicinal chemistry at the university of Orléans with Pr Sylvain Routier. In 2010, he was appointed assistant professor in the group of Pr Marc Lemaire at the University of Lyon. He is now associate professor in the same team. His current research is focused on the development of original catalytic methods for the valorization of biomass (vegetable oils, sugars and polyols, etc.) and CO_2, notably through organocatalysis.