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Short communication

Synthesis and in vitro *Trichomonacidal* activities of some new dialkylperoxides and 1,2,4-trioxanes

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Abstract – Two series of three trioxanes and 18 disubstituted peroxides were synthesised and evaluated for their in vitro trichomonacidal activity against *Trichomonas vaginalis*. The most active compound, 2-methylprop-2-yl 2-methoxyeth-1-yl peroxide exhibited an IC_{50} value of 1.0±0.2 μM whereas other dialkyl peroxides had various IC_{50} values which could not be correlated to their molecule structure. The best compound was about five times more active than metronidazole. The amount of generated oxygen or free radicals cannot explain completely the activity suggesting another way of action for these compounds on *T. vaginalis*. © 2001 Éditions scientifiques et médicales Elsevier SAS

peroxides / *Trichomonas vaginalis* / metronidazole / trioxanes

1. Introduction

Trichomonas vaginalis, which affects at least 170 million individuals globally, may increase the risk of transmission of human immunodeficiency virus (HIV) [1] and predispose women to premature rupture of membrane and early labour. Chapman [2] has shown that these microaerophilic protozoa consumed O_2 (6.9 μM min^{-1} per 10^6 organisms) as in vagina, which is not a strictly anaerobic area to produce hydrogen peroxide in a small amount. At high concentrations of O_2 (>120 μM) *T. vaginalis* growth was inhibited. Ellis [3] indicated that the susceptibility of *T. vaginalis* to high O_2 concentration is due to a lack of adequate peroxide reducing enzymes, catalase and peroxidase.

In this context and in connection with a research programme on peroxide chemistry and biological activities, we have considered that oxidative compounds such as 1,2,4-trioxanes and dialkyl peroxides may act as a potential antimicrobial agents against *T. vaginalis*. Analog compounds have been found having interesting activities against other protozoa such as *Toxoplasma gondii* and *Plasmodium* sp. [4–6]. Some trioxanes were active in vivo on *Plasmodium berghei*/mice model [7, 8]. Since trioxanes have never been evaluated against *T. vaginalis*, we hypothesise that their oxidant properties could be of interest in antitrichomonal chemotherapy.

2. Chemistry

1,2,4-Trioxanes **1a** and **1b** (*table I*) are known compounds [9, 10] in opposite to 1,2,4-trioxane **1c** which was synthesised in two steps from nitrile **2** (*figure 1*).

Dialkyl peroxides **4a**–**i** (*table II*) were prepared from a coupling reaction between *tert*-butylhydroperoxide and alkyl bromides in the presence of sodium hydroxide [11]. Peroxides **5a**–**i** (*table II*) were synthesised from 2-methoxyprop-2-yl hydroperoxide, caesium hydroxide and alkyl bromide according to Dussault procedure [12] (*figure 2*). Alkyl bromides used for **4a**–**i** and **5a**–**f** were commercial compounds.

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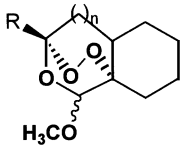
Table I. Trioxanes **1a–c**.



1a-c

1	a	b	c
R	CH_2Ome	CH_2Ph	CH_2Ph
n	1	2	1

3. Biological results and discussion

These products were synthesised to generate free radicals (e.g. $HO^{\bullet}$) when they are in biological media. The most active compound was **4d** belonging to the peroxide series. The corresponding methoxy **5d** was completely inactive. However, compounds **5a**, **5b** and **5c** were less active than **4a**, **4b** and **4c** suggesting that the presence of a methoxy group is not determined for antiparasitic activity.

Among the trioxane series, **1a–c**, **1a** presented weak parasiticidal activities (*table III*), probably because it has the lower MW and is the most soluble.

Among the peroxide **4** series, all tested compounds had an activity from weak (**4b**, **4g–i**) to equivalent or better than metronidazole (**4a** and **4c–f**). They are more active than the corresponding substituted compound of the perketal **5** series but **4e** and **5e** together demonstrated a high level of activity (*table III*). The amount of generated oxygen or free radicals could not alone explain the trichomonocidal activity of these compounds. The reason of the activity of peroxide on *T. vaginalis* is not clear and the higher activity of **5e** and **5g** by comparison with **4e** and **4g** suggests that another mechanism of action might be involved.

Clinical resistances of *T. vaginalis* to metronidazole are a rising problem [13, 14]. Synergisation of 5-nitroimidazole compounds by means of new compounds might be help in the fight against this worldwide sexually transmitted disease.

These results prompt us for further experiments with metronidazole-resistant *T. vaginalis* strain to access a potential synergism of activity between these dialkylperoxides and new ones with metronidazole. The evaluation of other derivatives was necessary to choose the best candidates for in vivo testing against *T. vaginalis*/mouse model.

4. Experimental protocols

The compounds were all identified by usual physical methods, i.e. ^{1}H-NMR, ^{13}C-NMR and elemental analysis.

^{1}H- and ^{13}C-NMR spectra were measured in $CDCl_3$ with a Bruker ARX 400 (400 and 100.6 MHz, for ^{1}H and ^{13}C, respectively). ^{1}H chemical shifts are reported in ppm from an internal standard TMS or of residual chloroform (7.27 ppm). The following abbreviations are used, m (multiplet); s (singlet); bs (broad singlet); d (doublet); t (triplet); q (quadruplet) and qt (quintuplet). ^{13}C chemical shifts are reported in ppm from the central peak of deuteriochloroform (77.14). Optical rotations were measured at 20 °C on a Perkin–Elmer 241 MC polarimeter in a 1 dm cell. Elemental analyses were performed with a Perkin–Elmer 240 analyser. Analytical thin-layer chromatography (TLC) was performed on Merck precoated silica gel 60F plates. Merck silica gel 60 (230–400 mesh) was used for column chromatography.

T. vaginalis, the CMP strain (Châtenay–Malabry, parasitology) was isolated from a woman in the year 1987 and stored as stabilate in liquid nitrogen with 6% dimethyl sulfooxide (DMSO) as cryoprotectant; it is a metronidazole-sensitive strain. Culture tubes with fresh TYM medium enriched with filtered horse serum 10% alone or with (in triplicate) the tested compound, were inoculated with 10^4 protozoa per

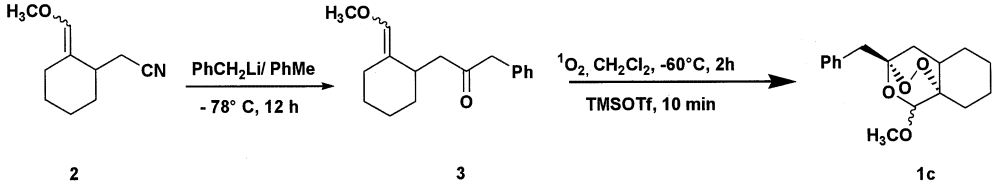
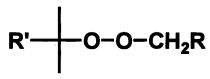


Figure 1. Synthesis of trioxane **1c**.

Table II. Dialkylperoxides **4** and **5**.



4 or 5

R	4	5
	R' = CH_3	R = OCH_3
C_6H_{13}	a	a
CH_2-Ph	b	b
$(CH_2)_2$Ph	c	c
CH_2-OMe	d	d
$(CH_2)_2$OPh	e	e
$(CH_2)_2$CN	f	f
	g	g
$(CH_2)_2$OH	h	
$(CH_2)_2$COOEt	i	
		h
		i

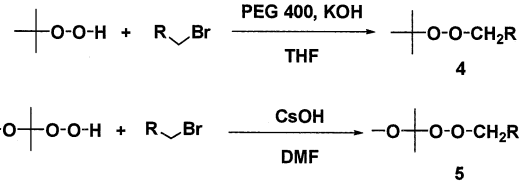


Figure 2. Synthesis of dialkylperoxides **4** and **5**.

mL^{-1} [15]. The tubes were cultivated in anaerobic conditions for 48 h at 35 °C and the number of parasites mL^{-1} in each tube determined with an haemocytometer (Kova slide 10, Boeringer). The results were estimated as the percentage of growth inhibition compared with untreated controls and plotted as profit value as a function of drug concentration ($n = 9$). The IC_{50} were interpolated from the corresponding dose–reponse curve. Metronidazole (8823 R.P.) was the reference compound.

4.1. Synthesis of trioxane ***1c***

4.1.1. 1-Phenyl-3-[2-(methoxymethylene)cyclohexyl]-propan-3-one ***(3)***

To a solution of nitrile **2** at −78 °C (*Z*/*E*, 3/7) [6] (0.35 g, 2.12 mmol) in 10 mL of toluene was added slowly under argon a solution of benzyllithium (5 mmol) in toluene (prepared from 1.2 mL of TMEDA, 3.125 mL of BuLi and 10 mL of toluene) [16]. The mixture was stirred over night at −78 °C and allowed to warm up to 20 °C. The solution was poured into a saturated NH_4Cl solution, extracted with ether (3×20 mL) and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (cyclohexane–AcOEt, 95:5) and gave 0.385 g of (*Z*)-**3** and (*E*)-**3** in a ratio 3/7.

Yield: 70%.

Anal. $C_{17}H_{22}O_2$. % Found (Calc.): C, 78.99 (79.07); H, 8.52 (8.53).

^{1}H-NMR δ 7.50–7.05 (m, 5H, Ar*H*), 5.70 (s, 0.3H, *H*C=), 5.60 (s, 0.7H, *H*C=), 3.75 (s, 0.6H, CH_2Ar), 3.65 (s, 1.4 H, CH_2Ar), 3.50 (s, 0.9H, OCH_3), 3.45 (s, 2.1H, OCH_3), 2.80–2.25 (m, 3H), 2.25–2.05 (m, 1H), 1.70–1.15 (m, 7H). ^{13}C-NMR δ 209.6, 139.5, 129.7 (2C) and 129.5 (2C), 128.8 (2C) and 128.6 (2C), 127.1 and 126.9, 59.5 and 59.4, 50.9 and 49.7, 45.0 and 44.9, 35.1 and 30.7, 33.7, 31.7, 28.2, 27.5, 27.1, 23.8, 23.5 and 22.1.

4.1.2. Trioxane ***1c***

A solution of **3** (0.360 g, 1.4 mmol) and Methylene Blue (2 mg) in dry CH_2Cl_2 was photooxygenated at −60 °C for 2 h after which time TMSOTf (0.1 mL) was added on the resulting mixture with stirring for 10 min at −60 °C and then neutralisation was achieved with a few drops of Et_3N. The organic layer was then washed with water and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by column chromatography (cyclohexane–AcOEt, 98:2) and gave 0.18 g of α-**1c** and β-**1c** in a 1/1 ratio.

Yield: 45%.Anal. $C_{17}H_{22}O_4$. % Found (Calc.): C, 70.01 (70.34); H, 7.42 (7.58).

^{1}H-NMR δ 7.30–7.00 (m, 5H, Ar*H*), 4.85 (d, $J = 1.5$ Hz, 0.5H, *H*COCH$_3$), 4.74 (s, 0.5H, *H*COCH$_3$), 3.15 (s, 1.5H, OCH_3), 3.10 (s, 1.5H,OCH_3), 3.05–2.90 (m, 1H),

2.90–2.75 (m, 1H), 2.20–1.80 (m, 2H), 1.75–1.10 (m, 8H), 1.00–0.80 (m, 1H). ^{13}C-NMR δ 135.2 (4C), 131.0 (6C), 127.0 (2C), 105.8, 102.2, 101.1, 100.5, 75.7, 75.1, 55.0, 54.8, 43.2 (2C), 35.8, 35.4, 35.2, 31.0, 29.8, 29.4, 29.3, 28.4, 25.1 (2C), 22.7, 20.7.

4.2. Synthesis of peroxides **4a**–**i**

Peroxides **4a**–**i** were synthesised by the following literature [11].

4.2.1. 2-Methylprop-2-yl hept-1-yl peroxide (**4a**) [11]

Yield: 64%. ^{1}H-NMR δ 3.95 (t, 2H, $J = 6.3$ Hz, OCH_2), 1.65–1.45 (m, 2H), 1.40–1.10 (m, 8H), 1.25 (s, 9H, (CH_3)$_3$C), 0.85 (t, 3H, $J = 6.6$ Hz, CH_3CH$_2$). ^{13}C-NMR δ 79.4, 74.8, 32.0, 29.4, 28.3, 27.1, 26.5 (3C), 22.9, 14.1.

4.2.2. 2-Methylprop-2-yl 2-phenyleth-1-yl peroxide (**4b**)

Yield: 81%.

Anal. $C_{12}H_{18}O_2$. % Found (Calc.): C, 74.28 (74.22); H, 9.38 (9.28).

^{1}H-NMR δ 7.40–7.20 (m, 5H, ArH), 4.15 (t, 2H, $J = 5.9$ Hz, CH_2O), 2.95 (t, 2H, $J = 5.9$ Hz, CH_2Ar), 1.20 (s, 9H, (CH_3)$_3$C). ^{13}C-NMR ($CDCl_3$) δ 138.6, 129.0 (2C), 128.4 (2C), 126.2, 82.3, 75.7, 34.6, 26.4 (3C).

4.2.3. 2-Methylprop-2-yl 2-phenylprop-1-yl peroxide (**4c**)

Yield: 72%.

Anal. $C_{13}H_{20}O_2$. % Found (Calc.): C, 75.09 (75.00); H, 9.75 (9.61).

^{1}H-NMR δ 7.40–7.15 (m, 5H, ArH), 4.00 (t, 2H, $J = 7.7$ Hz, CH_2O), 2.70 (t, 2H, $J = 7.7$ Hz, CH_2Ar), 1.95 (tq, 2H, CH$_2$CH_2CH$_2$), 1.30 (s, 9H, (CH_3)$_3$C). ^{13}C-NMR δ 141.8, 128.4 (4C), 125.9, 80.1, 74.2, 32.4, 29.6, 26.4 (3C).

4.2.4. 2-Methylprop-2-yl 2-methoxyeth-1-yl peroxide (**4d**)

Yield: 66%.

Anal. $C_7H_{16}O_3$. % Found (Calc.): C, 56.72 (56.76); H, 10.95 (10.81).

^{1}H-NMR δ 4.10 (t, 2H, $J = 4.6$ Hz, CH_2OO), 3.60 (t, 2H, $J = 4.6$ Hz, CH_2O), 3.40 (s, 3H, OCH_3), 1.25 (s, 9H, (CH_3)$_3$C). ^{13}C-NMR δ 74.5, 70.0, 59.0, 42.6, 26.3 (3C).

4.2.5. 2-Methylprop-2-yl 3-phenoxyprop-1-yl peroxide (**4e**)

Yield: 70%.

Anal. $C_{13}H_{20}O_3$. % Found (Calc.): C, 69.72 (69.64); H, 9.01 (8.93).

Table III. In vitro *Trichomonacidal* activities of peroxides **1**, **4** and **5**.

References	Formula	M_W	*T. vaginalis* IC_{50} (μM) ± S.D.
1a	$C_{12}H_{20}O_5$	212	24.4 ± 3.4
1b	$C_{18}H_{24}O_4$	304	> 328
1c	$C_{17}H_{22}O_4$	290	> 344
4a	$C_{11}H_{24}O_2$ [a]	188	2.6 ± 0.3
4b	$C_{12}H_{18}O_2$	194	30.9 ± 3.4
4c	$C_{18}H_{20}O_2$	268	3.4 ± 0.4
4d	$C_7H_{16}O_3$ [a]	148	1.0 ± 0.2
4e	$C_{13}H_{20}O_3$ [a]	224	2.4 ± 0.3
4f	$C_8H_{15}NO_2$	157	5.1 ± 0.6
4g	$C_{15}H_{26}O_2$	238	14.7 ± 1.9
4h	$C_7H_{16}O_3$	148	7.4 ± 0.9
4i	$C_{10}H_{20}O_4$	204	53.9 ± 7.0
5a	$C_{11}H_{24}O_3$	204	73.5 ± 8.9
5b	$C_{12}H_{18}O_3$	210	57.1 ± 6.6
5c	$C_{13}H_{20}O_3$	224	> 443
5d	$C_7H_{16}O_4$	164	> 609
5e	$C_{13}H_{20}O_4$ [a]	240	1.4 ± 0.2
5f	$C_8H_{15}NO_3$	173	57.8 ± 7.3
5g	$C_{15}H_{26}O_3$	254	3.5 ± 0.4
5h	$C_9H_{18}O_3$	174	> 575
5i	$C_9H_{20}O_3$ [a]	176	2.1 ± 0.3
Metronidazole no. 8823 RP (Flagyl®)	$C_6H_9N_3O_3$	171	5.8 ± 0.6

[a] Significantly more active than metronidazole ($P < 0.05$).

^{1}H-NMR δ 7.20–7.00 (m, 2H, Ar*H*), 6.90–6.75 (m, 3H, Ar*H*), 4.00 (t, 2H, $J = 5.5$ Hz, CH_2OO), 3.75 (t, 2H, $J = 5.5$ Hz, CH_2OAr), 1.90 (qt, 2H, $J = 5.5$ Hz, $CH_2CH_2CH_2$), 1.20 (s, 9H, $(CH_3)_3C$). ^{13}C-NMR δ 143.1, 129.5 (2C), 120.7, 114.7 (2C), 79.4, 71.3, 64.6, 28.3, 26.3 (3C).

*4.2.6. 2-Methylprop-2-yl 3-carbonitrile prop-1-yl peroxide (**4f**)*

Yield: 66%.

Anal. $C_8H_{15}NO_2$. % Found (Calc.): C, 61.47 (61.15); H, 9.89 (9.55); N, 8.05 (8.28).

^{1}H-NMR δ 4.00 (t, 2H, $J = 6.3$ Hz, CH_2O), 2.45 (t, 2H, $J = 6.3$ Hz, CH_2CN), 1.95 (qt, 2H, $J = 6.3$ Hz, $CH_2CH_2CH_2$), 1.20 (s, 9H, $(CH_3)_3C$). ^{13}C-NMR δ 119.3, 80.4, 72.2, 26.3 (3C), 24.5, 14.2.

*4.2.7. 2-Methylprop-2-yl 2-[(1S)-6,6-dimethyl-bicyclo[3.1.1]hept-2-en-2-yl]eth-1-yl peroxide (**4g**)*

Yield: 44%.

Anal. $C_{15}H_{26}O_2$. % Found (Calc.): C, 75.65 (75.58); H, 10.89 (10.99).

^{1}H-NMR δ 5.30–5.20 (m, 1H, C=C*H*), 3.90 (t, 2H, $J = 7.2$ Hz, CH_2O), 2.35–1.95 (m, 5H), 1.25 (s, 3H), 1.25 (s, 9H, $(CH_3)_3C$), 1.15 (d, 1H, $J = 8{,}4$ Hz), 0.80 (s, 3H). ^{13}C-NMR δ 144.6, 118.0, 80.0, 73.3, 46.0, 40.8, 38.0, 35.3, 31.7, 31.4, 26.4 (4C), 21.2. $[\alpha]_D = -27$, 17° ($c = 0$, 92, $CHCl_3$).

*4.2.8. 2-Methylprop-2-yl 3-hydroxyprop-1-yl peroxide (**4h**)*

Yield: 74%.

Anal. $C_7H_{16}O_3$. % Found (Calc.): C, 56.84 (56.76); H, 11.01 (10.81).

^{1}H-NMR δ 4.05 (t, 2H, $J = 6.3$ Hz, CH_2OO), 3.70 (t, 2H, $J = 6.3$ Hz, CH_2OH), 2.20 (bs, 1H, O*H*), 1.85 (qt, 2H, $J = 6.3$ Hz, $CH_2CH_2CH_2$), 1.20 (s, 9H, $(CH_3)_3C$). ^{13}C-NMR δ 80.4, 72.9, 60.5, 31.3, 26.3 (3C).

*4.2.9. 2-Methylprop-2-yl 3-carboxilic acid ethyl ester propyl peroxide (**4i**)*

Yield: 57%.

Anal. $C_{10}H_{20}O_4$. % Found (Calc.): C, 58.42 (58.82); H, 9.51 (9.80).

^{1}H-NMR δ 3.90 (q, 2H, $J = 7.1$ Hz, OCH_2CH$_3$), 3.85 (t, 2H, $J = 7.7$ Hz, CH_2OO), 2.25 (t, 2H, $J = 7.7$ Hz, CH_2CO), 1.70 (qt, 2H, $J = 7.7$ Hz, $CH_2CH_2CH_2$), 1.15 (t, 3H, $J = 7.1$ Hz, CH_3CH$_2$), 1.10 (s, 9H, $(CH_3)_3C$). ^{13}C-NMR δ 173.2, 80.2, 73.7, 60.4, 30.9, 26.3 (3C), 23.5, 14.2.

*4.3. Synthesis of peroxides **5a–i***

Peroxides **5a–i** were synthesised according to the following literature [12].

*4.3.1. 2-Methoxyprop-2-yl hept-1-yl peroxide (**5a**)*

Yield: 77%.

Anal. $C_{11}H_{24}O_3$. % Found (Calc.): C, 64.41 (64.67); H, 12.21 (11.84).

^{1}H-NMR δ 3.95 (t, 2H, $J = 6.6$ Hz, CH_2OO), 3.25 (s, 3H, OCH_3), 1.55 (m, 2H), 1.30 (s, 6H, $(CH_3)_2C$), 1.35–1.10 (m, 8H), 0.80 (t, 3H, $J = 6.4$ Hz, CH_3CH$_2$). ^{13}C-NMR δ 104.1, 74.7, 48.6, 31.6, 29.2, 29.0, 27.7, 25.9, 22.4 (2C), 13.7.

*4.3.2. 2-Methoxyprop-2-yl 2-phenyleth-1-yl peroxide (**5b**)*

Yield: 36%.

Anal. $C_{12}H_{18}O_3$. % Found (Calc.): C, 68.20 (68.54); H, 8.48 (8.63).

^{1}H-NMR δ 7.25 (m, 5H, ArH), 4.25 (t, 2H, $J = 7.2$ Hz, CH_2O), 3.35 (s, 3H, OCH_3), 3.00 (t, 2H, $J = 7.2$ Hz, CH_2Ar), 1.40 (s, 6H, $(CH_3)_2C$). ^{13}C-NMR δ 138.3, 128.9 (2C), 128.4 (2C), 126.3, 104.7, 75.7, 49.2, 34.6, 22.8 (2C).

*4.3.3. 2-Methoxyprop-2-yl 3-phenylprop-1-yl peroxide (**5c**)*

Yield: 76%.

Anal. $C_{13}H_{20}O_3$. % Found (Calc.): C, 69.44 (69.61); H, 8.76 (8.99).

^{1}H-NMR ($CDCl_3$), δ 7.30–7.15 (m, 5H, ArH), 4.05 (t, 2H, $J = 6.3$ Hz, CH_2O), 3.30 (s, 3H, OCH_3), 2.75 (t, 2H, $J = 7.5$ Hz, CH_2Ar), 2.00–1.90 (m, 2H, $CH_2CH_2CH_2$), 1.45 (s, 6H, $(CH_3)_2C$). ^{13}C-NMR δ 141.6, 128.5 (4C), 125.9, 104.6, 74.0, 49.0, 32.3, 29.6, 22.8 (2C).

*4.3.4. 2-Methoxyprop-2-yl 3-methoxymeth-1-yl peroxide (**5d**)*

Yield: 40%.

Anal. $C_7H_{16}O_4$. % Found (Calc.): C, 51.35 (51.20); H, 9.62 (9.82).

^{1}H-NMR δ 4.05 (t, 2H, $J = 4.7$ Hz, CH_2OO), 3.50 (t, 2H, $J = 4.7$ Hz, CH_2O), 3.25 (s, 3H), 3.20 (s, 3H), 1.30 (s, 6H, $(CH_3)_2C$). ^{13}C-NMR δ 104.8, 74.3, 69.7, 58.9, 49.2, 22.6 (2C).

*4.3.5. 2-Methoxyprop-2-yl 3-phenoxyprop-1-yl peroxide (**5e**)*

Yield: 80%.

Anal. $C_{13}H_{20}O_4$. % Found (Calc.): C, 64.81 (64.98); H, 8.28 (8.39).

^{1}H-NMR δ 7.25 (t, 2H, Ar*H*), 6.9 (m, 3H, ArH), 4.20 (t, 2H, $J = 6.2$ Hz), 4.10 (t, 2H, $J = 6.2$ Hz), 3.30 (s, 3H, OCH_3), 2.15 (q, 2H, $J = 6.2$ Hz, $CH_2CH_2CH_2$), 1.40 (s, 6H, $(CH_3)_2C$). ^{13}C-NMR δ 158.8, 129.6 (2C), 121.0, 114.7 (2C), 108.4, 73.8, 72.1, 27.8, 21.5 (2C). The signal of the methoxy group is unapparent on the spectra.

*4.3.6. 2-Methoxylprop-2-yl 3-carbonitrile prop-1-yl peroxide (**5f**)*

Yield: 70%.

Anal. $C_8H_{15}NO_3$. % Found (Calc.): C, 55.21 (55.47); H, 8.50 (8.73); N, 8.10 (8.09).

^{1}H-NMR δ 4.05 (t, 2H, $J = 5.8$ Hz, CH_2OO), 3.25 (s, 3H, OCH_3), 2.45 (t, 2H, $J = 7.2$ Hz, CH_2CN), 2.05–1.85 (qt, 2H, $CH_2CH_2CH_2$), 1.30 (s, 6H, $(CH_3)_2C$). ^{13}C-NMR δ 119.2, 104.9, 72.4, 49.2, 24.4, 22.6 (2C), 14.0.

*4.3.7. 2-Methoxyprop-2-yl 2-[(1S)-6,6-dimethyl-bicyclo[3.1.1]hept-2-en-2-yl]-eth-1-yl peroxide (**5g**)*

Yield: 44%.

Anal. $C_{15}H_{26}O_3$. % Found (Calc.): C, 70.54 (70.83); H, 10.00 (10.30).

^{1}H-NMR δ 5.35–5.20 (m, 1H, *H*C=), 4.00 (t, 2H, $J = 7.3$ Hz, OCH_2), 3.25 (s, 3H, OCH_3), 2.35–2.10 (m, 5H), 2.05–1.95 (m, 2H), 1.35 (s, 6H, $(CH_3)_2C$), 1.20 (s, 3H), 1.10 (d, 1H, $J = 8.6$ Hz), 0.80 (s, 3H). ^{13}C-NMR δ 144.4, 118.1, 104.4, 73.3, 49.1, 45.9, 40.7, 37.9, 35.3, 31.6, 31.3, 26.3, 22.7 (2C), 21.1. $[\alpha]_D = -18.3$ (*c* 0.71, CH_2Cl_2).

*4.3.8. 2-Methoxyprop-2-yl 3-methylbut-2-en-1-yl peroxide (**5h**)*

Yield: 50%.

Anal. $C_9H_{18}O_3$. % Found (Calc.): C, 61.89 (62.04); H, 10.33 (10.41).

^{1}H-NMR δ 5.30 (m, 1H, *H*C=), 4.50 (d, 2H, $J = 7.2$ Hz, OCH_2), 3.30 (s, 3H, OCH_3), 1.75 (s, 3H), 1.70 (s, 3H), 1.40 (s, 6H). ^{13}C-NMR δ 139.8, 118.0, 104.4, 71.2, 48.9, 25.6, 22.6 (2C), 17.9.

*4.3.9. 2-Methoxyprop-2-yl 3-methylbut-1-yl peroxide (**5i**)*

Yield: 30%.

Anal. $C_9H_{20}O_3$. % Found (Calc.): C, 61.01 (61.33); H, 11.12 (11.44).

^{1}H-NMR δ 4.0 (t, 2H, $J = 6.6$ Hz, CH_2O), 3.3 (s, 3H, OCH_3), 1.75–1.55 (m, 1H), 1.5–1.4 (m, 2H), 1.35 (s, 6H, $(CH_3)_2C$), 0.9 (d, 6H, $J = 6$ Hz, $(CH_3)_2CH$). ^{13}C-NMR δ 108.3, 73.8, 36.5, 25.3, 22.6 (2C), 21.5 (2C). The signal of the methoxy group is unapparent on the spectra.

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