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Novel Hydroperoxydioxolanes and -dioxanes by Hydroperoxide Rearrangement and Ozonolysis

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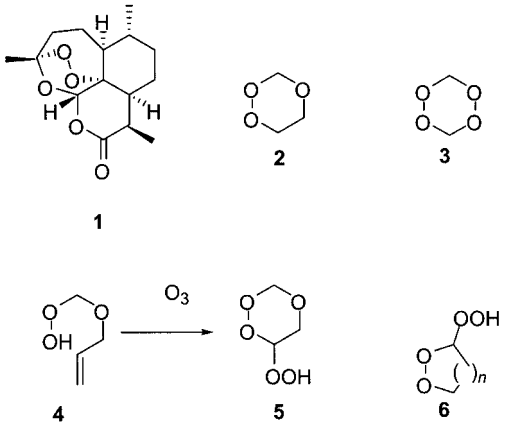
1-Indanols and 1-tetralols **8** with alkenyl substituents in the 1-position have been converted into the corresponding 1-hydroperoxides **9** by substitution under neutral conditions. Ozonolysis of the products gave rise to the formation of spiro-1,2-dioxolane and spiro-1,2-dioxane hydroperoxides **12**. Alternative treatment of these 1-indanols and 1-tetralols **8** with hydrogen peroxide under acidic conditions caused substitution and hydroperoxide rearrangement to yield chroman-2-yl hydroperoxides **16** or open-chain unsaturated geminal bis-hydroperoxides **21**. Ozonolysis of these products resulted in the formation of novel spiro-chromanes **18** and **20** with two oxygen atoms in the second ring or 3,5-bis(hydroperoxy)-1,2-dioxolanes or 3,6-bis(hydroperoxy)-1,2-dioxanes **23**, respectively. All the products showed feeble antimalaria activity against chloroquine-resistant *plasmodium falciparum*.

Introduction

Cyclic peroxides occur widely in nature and have attracted interest as pharmaceutically active compounds, for example, with antimalarial, antibiotic or antitumor properties.[1] They have gained a renaissance in the last 15 years. Artemisinin (qinghaosu) (**1**) (Scheme 1), a prominent member of this class of compound, exhibits high potency against drug-resistant forms of malaria strains such as *Plasmodium falciparum*.[2] It contains a 1,2,4-trioxane ring **2** incorporated into a polycyclic saturated terpenoid structure. Although the mechanism of its action is still under discussion,[3] it has been proposed that homolytic cleavage of the peroxide moiety by heme Fe^{II} and the formation of a carbon-centered radical are the first steps in the destruction of the parasite in the erythrocyte.[4,5] Thus many more simple analogues of Artemisinin containing a cyclic peroxide moiety have been synthesized and tested, as well as naturally occurring monocyclic 1,2-dioxanes,[6,7] to determine any structure–activity relationships. This research revealed that 1,2,4-trioxanes **2**[2,8], 1,2,4,5-tetroxanes **3**[2] and the homologous 1,2,4,5-tetraoxacycloalkanes exhibit significant antimalarial activity.[9] The latter two classes contain an acetal-like geminal bis-peroxide moiety. A similar structural element, in which one of the peroxy moieties is, however, exocyclic, is found in 6-hydroperoxy-1,2,4-trioxanes **5**, which were synthesized by ozonolysis of α-allyloxymethyl hydroperoxides **4**:[10] The primary ozonide of **4** is cleaved to an intermediate carbonyl oxide which undergoes electrophilic cyclization. In a similar way, bicyclic hydroperoxy peroxides have been obtained from unsaturated cyclic hydroperoxy acetals.[11] The starting materials for these syntheses were prepared from the reaction of allylic alcohols with carbonyl oxides formed by ozonolysis of enol ethers or from the ozonolysis of unsaturated enol ether, respectively. In general, the electrophilic cyclization of alkenyl hydroperoxides with ozone or other electrophiles, such as halogens, *m*-chloroperbenzoic acid or mercury acetate, is a powerful tool for the synthesis of cyclic peroxides.[9,11–14]



Scheme 1.

Results and Discussion

Herein we report the synthesis of novel hydroperoxy-peroxide structures **6** (n = 1, 2) (Scheme 1) of the 1,2-dioxolane and 1,2-dioxane series by electrophilic cyclization of inter-

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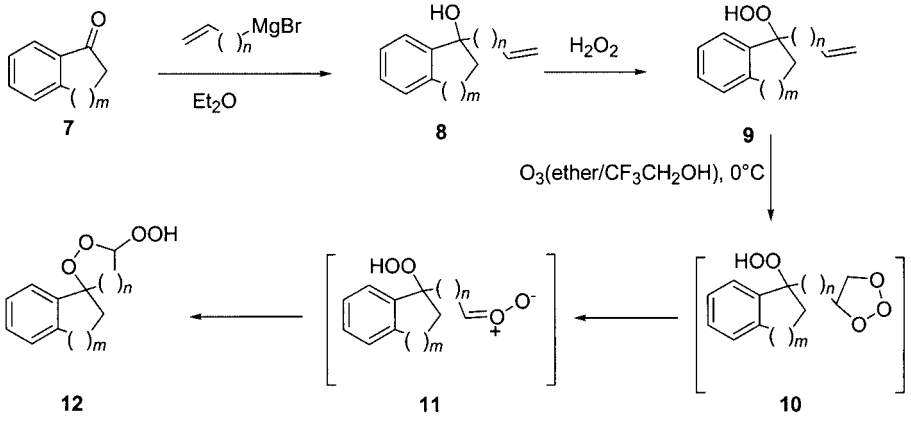


Scheme 2.

mediate carbonyl oxides obtained by ozonolysis. Suitable starting materials were obtained from 1-allyl- or 1-homoallyl-indan-1-ols and -1,2,3,4-tetrahydronaphthalenes **8** (n = 1,2), which are readily available through the Grignard reaction of the corresponding ketones **7** (Scheme 2). These alcohols **8** were transformed into the corresponding hydroperoxides **9** by nucleophilic substitution with aqueous hydrogen peroxide (70%). Treatment of solutions of the resulting hydroperoxides **9** with ozone in diethyl ether/trifluoroethanol resulted in the formation of the desired spirohydroperoxydioxolanes and spirohydroperoxydioxanes **12** (m = 1, 2), respectively (Table 1). This electrophilic cyclization reaction is likely to proceed via the extrusion of formaldehyde from primary ozonides **10** to give carbonyl oxides **11**. 3-Hydroxydioxolanes or -dioxanes analogous to **12** were not observed, suggesting that cycloreversion of the primary ozonide **10** proceeded regioselectively to form the aldehyde *O*-oxide.

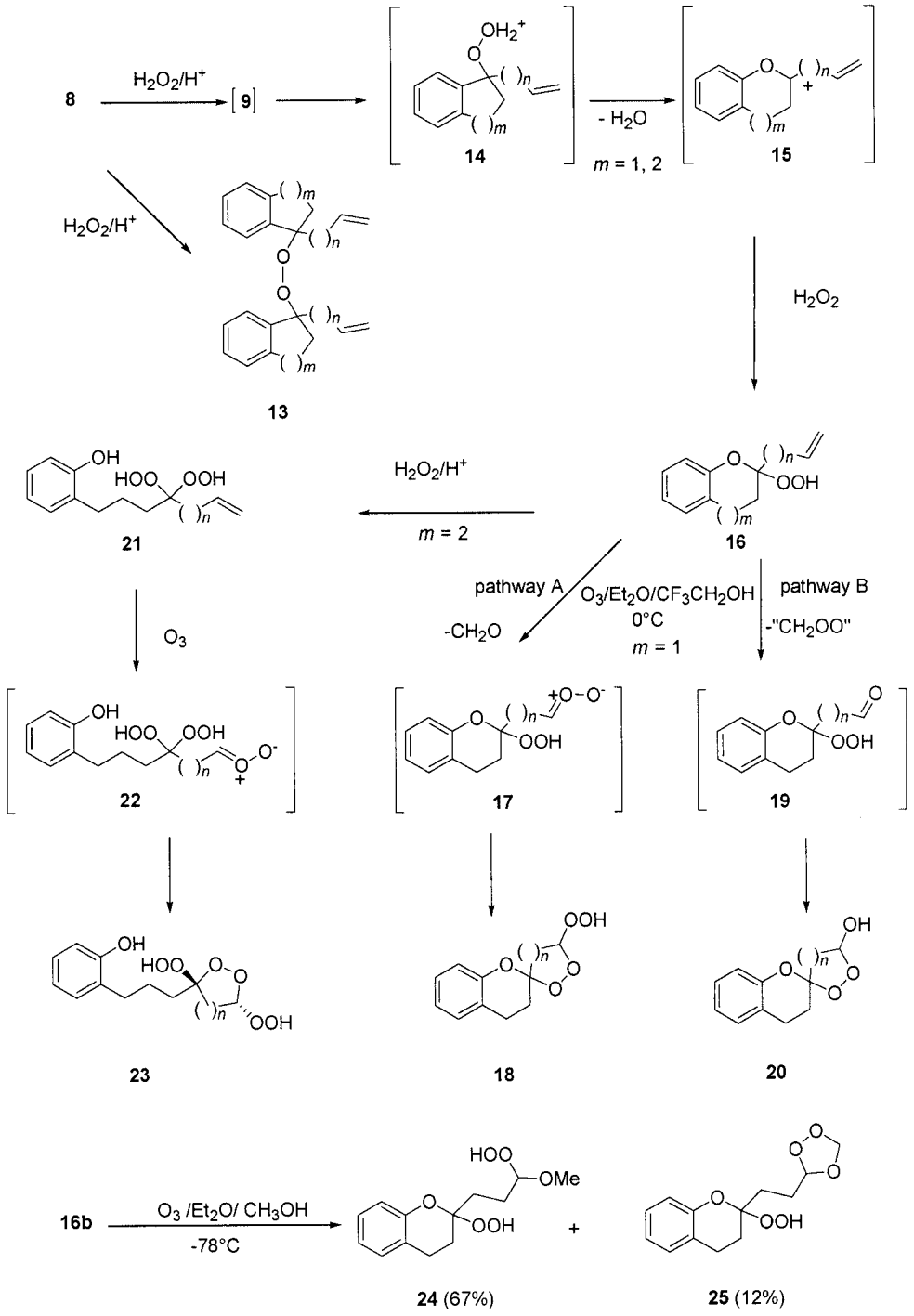
Table 1. Starting materials **8** and yields (in parentheses) of products **9a**–**d** and **12a**–**d**.

Entry	m	n	**8**	Yields (%) **9**	**12**	*dr* of **12**
1	1	1	**a**	**a** (58)	**a** (71)	1:1
2	1	2	**b**	**b** (55)	**b** (48)	2:1
3	2	1	**c**	**c** (54)	**c** (21)	1:1
4	2	2	**d**	**d** (27)	**d** (26)	2:1

The reaction sequence of nucleophilic substitution of a hydroxy group by hydrogen peroxide followed by ozonolysis may also be applied to the synthesis of other more complex spirohydroperoxydioxolanes and -dioxanes when the first step is catalyzed by acids. By analogy with our previously developed hydroperoxide rearrangement under ring-enlargement conditions,[15,16] the hydroperoxides **9**, which are formed in the first substitution step from the alcohols **8**, undergo rearrangement into chroman-2-yl hydroperoxides **16** in the case of m = 1 or are further ring-opened to geminal bis-hydroperoxides **21** if m = 2 (Scheme 3). In the case of the homoallyl and the pent-1-en-5-yl-substituted alcohols **8b** and **8c** (n = 2, 3; see Table 2) a symmetric peroxide **13** was obtained as a byproduct of the reaction with hydrogen peroxide under acidic conditions, that is, the hydroperoxide **9** reacted with the intermediate carbenium cation formed from the alcohol **8** without the involvement of a hydroperoxide rearrangement.

The alkenyl hydroperoxides **16** and **21** were further submitted to ozonolysis in order to obtain cyclization products consisting of a hydroperoxyl-peroxide ring moiety of the general structure **6** by electrophilic cyclization (Table 2). Ozonolysis of the chromanyl hydroperoxides **16** (m = 1) in diethyl ether/trifluoroethanol at 0 °C provided spiro-hydroperoxy-peroxides **18** and spiro-peroxides **20**, depending on how the primary ozonides formed from **16** undergo 1,3-diopolar cycloreversion: either the carbonyl oxide **17** and formaldehyde were formed (pathway A) leading to the hydroperoxide **18** after cyclization or cleavage of the primary ozonide gave rise to the aldehyde **19** (pathway B), which cyclized to the hydroxy product **20**.

After ozonolysis of **16a** (m = 1, n = 1) only the formation of hydroperoxydioxolane **18a** was observed. In the case of **16b** (m = 1, n = 2) and **16e** (m = 1, n = 3) both cyclization products **18b/20b** and **18e/20e**, respectively, were obtained (see Table 2). Similar behavior was observed in the cyclization of unsaturated hydroperoxy acetals in the presence of ozone.[10] Unlike in the other cases, a mixture of stereoisomers was formed in the case of the seven-membered ring **18e** which could be partially separated by flash chromatography. Byproducts, which were probably polymeric peroxides, were formed in all cases, but no attempt was made to isolate them. An attempt to ozonolyze the alkenyl hydroperoxide **16b** in methanol led to alternative chromanyl hydroperoxides **24** (67%) and **25** (12%). The formation of **24** demonstrates the preferred cleavage of the primary ozonide derived from **16b** to yield an intermediate **17** (n = 2), similar to pathway A, followed by intermolecular trapping with methanol. The byproduct **25** may be formed either by the dipolar cycloaddition reaction of **17** and formaldehyde or by the reaction of the intermediate **19** with "CH_2OO". The effect of solvents on the outcome of the ozonolysis of **16** is in accordance with results found by other groups with other cases.[10]



Scheme 3.

Table 2. Products **9e**, **16**, **18**, **20**, **21** and **23** and their yields (in parentheses) obtained from alcohols **8** according to Scheme 3.

Entry	*m*	*n*	**8**	Yields (%) **9**	**16**	**18**	**20**	**21**	**23**
1	1	1	**a**		**a** (45)	**a** (18)[a]			
2	1	2	**b**		**b** (67)[b]	**b** (12)[a]	**b** (17)[a]		
3	1	3	**e**	**e** (16)	**e** (21)[c]	**e** (49)[d]	**e** (15)[e]		
4	2	1	**c**					**c** (41)	**c** (22)
5	2	2	**d**					**d** (31)	**d** (28)

[a] One diastereomer. [b] Formed along with 10% peroxide **13b**. [c] Formed along with 22% peroxide **13e**. [d] Two diastereomers (*dr* = 7:3). [e] Two diastereomers (*dr* = 1:1).

Ozonolysis of the geminal bis-hydroperoxides **21** led to the formation of bis(hydroperoxy)dioxanes and -dioxolanes **23**. Thus an intermediate carbonyl oxide **22** must be formed from the primary ozonide, which cyclizes by nucleophilic attack of the hydroperoxy group at the carbonyl oxide carbon atom similarly to pathway A. Again just one diastereomer was formed. NOE measurements of the isolated dioxolane **23c** (n = 1) suggest that the two hydroperoxy groups are *trans* to each other.

Typical signals of hydroperoxidic and peroxidic products were found in the ^{1}H and ^{13}C NMR spectra. The ^{1}H chemical shift of the OOH group of the alkenyl hydroperoxides **9** was observed at around 7 ppm, whereas the corresponding ^{13}C signals of the C-1 atom were determined at δ = 85 (**9a**,**b**) and 95 ppm (**9c**,**d**). For the other hydroperoxides a downfield shift of the ^{1}H NMR signals to 8 (**16**), 9.5 (**12**, **18**) and 10–11 ppm (**21**, **23**) was found and in the ^{13}C NMR spectra a shift to 105-114 ppm.

The hydroperoxides and peroxides, **9c**, **9d**, **12c**, **12d**, **18a**, **18b**, **18e**, **20b**, **21c**, **21d**, **23c** and **23d**, were tested for their antimalarial activity against *Plasmodium falciparum* 3D7 and the chloroquine-resistant strain *Plasmodium falciparum* K1. The best results were obtained with **9c** (ED_{50} = 0.7 μg/ml for *P.f. 3D7*, ED_{50} = 0.5 μg/ml for *P.f* K1) and **12d** (ED_{50} = 1.8 μg/ml for *P.f.* 3D7, ED_{50} = 0.8 μg/ml for *P.f.* K1). The least active compounds against *P. falciparum* 3D7 (ED_{50} > 30 μg/ml) were compounds **18** and **20**.

In conclusion, we have developed a convenient method for the synthesis of novel 1,2-dioxolanes and 1,2-dioxanes. The procedures were based either on cyclization following ozonolysis of alkenyl hydroperoxides obtained from the corresponding alcohols with hydrogen peroxide or on hydroperoxide rearrangement by ring expansion followed by ozonolysis.

Experimental Section

General: Melting points were determined with a hot-stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively, with TMS as the internal standard. Silica gel (0.04–0.063) was used for column chromatography. Starting materials **8**, except for **8b**,[17] are new and were prepared by Grignard reaction of the corresponding ketones **7** (see the Supporting information). All other reagents were reagent grade and were used without purification. Ozonolysis was carried out using Fischer Ozon-generator, Modell 503.

Caution: *All safety precautions should be taken when working with highly concentrated hydrogen peroxide. Since organic peroxides are potentially hazardous compounds, they must be handled with due care; avoid exposure to strong heat or light, mechanical shock, oxidizable organic materials or transition-metal ions. No particular difficulties were experienced in handling any of the new peroxides synthesized in this work using the reaction scales and procedures described below together with the safeguard mentioned above.*

General Procedure for the Preparation of 9a–d (Table 1): Aqueous hydrogen peroxide (5 mL, 70%) was added to **8** (10 mmol) whilst stirring and with ice-cooling. After 15 min the mixture was warmed to room temperature and stirred for 2 d. After dilution of the mixture with water (20 mL), extraction with diethyl ether (3 × 25 mL), washing with saturated aqueous $NaHCO_3$ (25 mL) and with water, the organic phase was dried with Na_2SO_4. The solvent was removed under reduced pressure and the products were separated by column chromatography.

1-Allylindan-1-yl Hydroperoxide (9a): Colorless oil; yield 1.10 g (58%), R_f (hexane/EtOAc, 8:2) = 0.64. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.43 (m, 1 H), 7.21–7.35 (m, 4 H), 5.69–5.85 (m, 1 H), 5.05–5.20 (m, 2 H), 2.88–3.12 (m, 2 H), 2.60–2.86 (m, 2 H), 2.16–2.38 (m, 2 H) ppm. ^{13}C NMR (75.5 MHz, DMSO): δ = 145.5, 142.0, 133.4, 129.1, 126.3, 125.2, 124.3, 118.3, 95.0, 40.1, 33.7, 29.9 ppm. $C_{12}H_{14}O_2$ (190.26): calcd. C 75.76, H 7.42; found C 75.66, H 7.38.

1-But-3-enylindan-1-yl Hydroperoxide (9b): Colorless oil; yield 1.12 g (55%), R_f (hexane/EtOAc, 8:2) = 0.66. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.38 (m, 1 H), 7.19–7.33 (m, 4 H), 5.78–5.94 (m, 1 H), 4.92–5.09 (m, 2 H), 2.77–3.14 (m, 2 H), 2.14–2.43 (m, 4 H), 1.81–1.93 (m, 2 H) ppm. ^{13}C NMR (75.5 MHz, DMSO): δ = 147.0, 142.4, 138.5, 129.1, 126.3, 125.2, 124.2, 114.5, 95.4, 34.6, 34.1, 30.0, 28.4 ppm. $C_{13}H_{16}O_2$ (204.27): calcd. C 76.44, H 7.90; found C 76.31, H 7.77.

1-Allyl-1,2,3,4-tetrahydronaphthalen-1-yl Hydroperoxide (9c): Colorless oil; yield 1.10 g (54%), R_f (hexane/EtOAc, 7:3) = 0.5. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.44 (m, 1 H), 7.28 (s, 1 H), 7.01–7.17 (m, 3 H), 5.50–5.64 (m, 1 H), 4.94–5.00 (m, 2 H), 2.61–2.79 (m, 2 H), 2.58 (d, J = 8.29 Hz, 2 H), 1.64–1.95 (m, 4 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 138.8, 136.6, 133.1, 128.9, 127.5, 126.5, 125.8, 117.9, 83.9, 43.5, 29.9, 29.5, 19.6 ppm. $C_{13}H_{16}O_2$ (204.27): calcd. C 76.44, H 7.90; found C 76.74, H 7.88.

1-Butenyl-1,2,3,4-tetrahydronaphthalen-1-yl Hydroperoxide (9d): Colorless oil; yield 0.59 g (27%), R_f (hexane/EtOAc, 8:2) = 0.25. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61 (s, 1 H), 7.42–7.45 (m, 1 H), 7.14–7.17 (m, 2 H), 7.05–7.08 (m, 1 H), 5.68–5.80 (m, 1 H), 4.88–4.98 (m, 2 H), 2.61–2.81 (m, 2 H), 2.27–2.33 (m, 1 H), 1.82–1.99 (m, 7 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 139.4, 138.7, 137.6, 129.6, 128.1, 127.0, 126.6, 114.9, 84.9, 38.6, 30.8, 30.3, 28.7, 20.6 ppm. HRMS (ESI): calcd. for $C_{14}H_{19}O_2$ $[M + H]^+$: 219.1380; found 219.1384.

General Procedure for the Preparation of 9e, 13, 16 and 21 (Table 2): Concd. H_2SO_4 (1 drop) was added to a solution of **8** (10 mmol) in 70% aqueous hydrogen peroxide (10 mL) whilst stirring and ice-cooling. After 15 min the mixture was warmed to room temperature and stirred for 2 d. After dilution with water (20 mL), extraction with diethyl ether (3 × 25 mL), washing with saturated aqueous $NaHCO_3$ (25 mL) and with water, the organic phase was dried with Na_2SO_4. The solvent was removed under reduced pressure and the products were separated by column chromatography.

2-Allylchroman-2-yl Hydroperoxide (16a): Colorless oil; yield 0.93 g (45%), R_f (hexane/EtOAc, 8:2) = 0.51. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12 (s, 1 H), 6.91–7.04 (m, 2 H), 6.76–6.83 (m, 2 H), 5.70–5.86 (m, 1 H), 5.05–5.14 (m, 2 H), 2.77–2.86 (m, 1 H), 2.65–2.75 (m, 1 H), 2.44–2.61 (m, 2 H), 1.95–2.05 (m, 1 H), 1.67–1.81 (m, 1 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 152.0, 132.5 129.3, 127.5, 122.2, 121.4, 119.0, 117.1, 104.3, 40.3, 26.7, 20.9 ppm. HRMS (ESI): calcd. for $C_{12}H_{14}O_3$: 206.0943; found 206.0942.

2-But-3-enylchroman-2-yl Hydroperoxide (16b): Colorless oil; yield 1.48 g (67%), R_f (hexane/EtOAc, 8:2) = 0.33. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03 (s, 1 H), 7.00–7.13 (m, 2 H), 6.82–6.90 (m, 2 H), 5.78–5.93 (m, 1 H), 4.95–5.11 (m, 2 H), 2.75–2.89 (m, 1 H), 2.58 (ddd, J = 3.00, 6.03, 16.20 Hz, 1 H), 2.08–2.24 (m, 4 H), 1.91–2.02

(m, 1 H), 1.76–1.89 (m, 1 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 152.0, 138.0, 129.3, 127.5, 122.1, 121.3, 117.0, 114.9, 104.8, 34.7, 27.9, 26.7, 21.0 ppm. $C_{13}H_{16}O_3$ (220.27): calcd. C 70.89, H 7.32; found C 70.68, H 7.17.

2-Pent-4-enylchroman-2-yl Hydroperoxide (16e): Colorless oil; yield 0.49 g (21%), R_f (hexane/EtOAc 9:1) = 0.24. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (s, 1 H), 6.92–7.04 (m, 2 H), 6.74–6.83 (m, 2 H), 5.67–5.82 (m, 1 H), 4.86–5.01 (m, 2 H), 2.67–2.82 (m, 1 H), 2.45–2.56 (m, 1 H), 1.97–2.10 (m, 4 H), 1.69–1.84 (m, 2 H), 1.35–1.59 (m, 2 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 152.1, 138.4, 129.2, 127.4, 122.1, 121.2, 117.0, 115.1, 105.0, 35.1, 33.7, 26.6, 22.9, 21.1 ppm. $C_{14}H_{18}O_3$ (234.29): calcd. C 71.77, H 7.74; found C 71.79, H 7.77.

Bis(1-but-3-enylindan-1-yl) Peroxide (13b): Colorless oil; yield 0.37 g (10%), R_f (hexane/EtOAc, 8:2) = 0.79. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.09–7.24 (m, 6 H), 7.00–7.08 (m, 2 H), 5.69–5.85 (m, 2 H), 4.85–4.97 (m, 4 H), 2.60–2.93 (m, 4 H), 1.84–2.23 (m, 10 H), 1.62–1.78 (m, 2 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 144.8, 144.7, 143.8, 143.8, 139.1, 128.3, 128.1, 125.7, 125.7, 124.8, 124.7, 124.5, 124.5, 114.0, 92.9, 92.8, 35.1, 35.0, 34.8, 34.7, 30.1, 30.1, 28.5 (2×CH_2) ppm. $C_{26}H_{30}O_2$ (374.52): calcd. C 83.38, H 8.07; found C 83.06, H 8.36.

Bis(1-pent-4-enylindan-1-yl) Peroxide (13e): Colorless oil; yield 0.89 g (22%), R_f (hexane/EtOAc, 9:1) = 0.77. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.19–7.35 (m, 6 H), 7.10–7.18 (m, 2 H), 5.76–5.92 (m, 2 H), 4.98–5.10 (m, 4 H), 2.83–3.03 (m, 2 H), 2.69–2.82 (m, 2 H), 2.19–2.34 (m, 2 H), 1.96–2.14 (m, 8 H), 1.65–1.81 (m, 2 H), 1.40–1.56 (m, 2 H), 1.21–1.40 (m, 2 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 144.9, 144.8, 144.1, 144.0, 138.9, 128.2, 128.1, 125.7, 124.9, 124.8, 124.6, 124.5, 114.5, 93.2, 93.1, 35.5 (2×CH_2), 34.8, 34.7, 34.3, 30.2, 30.2, 23.5, 23.5 ppm. HRMS (ESI): calcd. for $C_{28}H_{34}O_2Na$: 425.2456; found 425.2456.

1-Pent-4-enylindan-1-yl Hydroperoxide (9e): Colorless oil; yield 0.35 g (16%), R_f (hexane/EtOAc, 9:1) = 0.19. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28 (s, 1 H), 7.23 (d, J = 7.53 Hz, 1 H), 7.08–7.20 (m, 3 H), 5.70 (dt, J = 6.78, 16.95 Hz, 1 H), 4.82–4.96 (m, 2 H), 2.88–3.01 (m, 1 H), 2.72 (ddd, J = 4.14, 9.04, 16.20 Hz, 1 H), 2.25 (ddd, J = 4.14, 8.66, 13.94 Hz, 1 H), 1.94–2.10 (m, 4 H), 1.69 (ddd, J = 4.52, 12.06, 13.56 Hz, 1 H), 1.36–1.52 (m, 1 H) 1.17–1.34 (m, 1 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 145.4, 142.6, 138.6, 129.0, 126.3, 125.1, 124.2, 114.8, 95.7, 34.9, 34.1, 34.0, 30.1, 23.4 ppm. HRMS (ESI): calcd. for $C_{14}H_{18}O_2Na$: 241.1204; found 241.1205.

2-[4,4-Bis(hydroperoxy)hept-6-enyl]phenol (21c): M.p. 80–81 °C; yield 0.91 g (41%), R_f (hexane/EtOAc, 7:3) = 0.1. ^{1}H NMR (300 MHz, DMSO): δ = 11.00 (s, 2 H), 9.23 (s, 1 H), 6.99–7.07 (m, 2 H), 6.70–6.81 (m, 2 H), 5.66–5.80 (m, 1 H), 5.05–5.13 (m, 2 H), 2.52 (t, J = 6.59 Hz, 2 H), 2.38 (d, J = 7.16 Hz, 2 H), 1.56–1.72 (m, 4 H) ppm. ^{13}C NMR (75.5 MHz, DMSO): δ = 155.1, 132.8, 129.8, 128.0, 126.8, 118.8, 118.3, 114.9, 110.8, 34.5, 29.7 (2×C), 23.2 ppm. $C_{13}H_{18}O_5$ (222.28): calcd. C 61.40, H 7.14; found C 61.62, H 7.02.

2-[4,4-Bis(hydroperoxy)oct-7-enyl]phenol (21d): M.p. 85–86 °C; yield 0.83 g (31%), R_f (hexane/EtOAc, 6:4) = 0.21. ^{1}H NMR (300 MHz, DMSO): δ = 10.82 (s, 2 H), 9.16 (s, 1 H), 6.91–7.00 (m, 2 H), 6.64–6.75 (m, 2 H), 5.68–5.80 (m, 1 H), 4.86–4.97 (m, 2 H), 2.41–2.52 (m, 2 H), 1.89–1.99 (m, 2 H), 1.49–1.61 (m, 6 H) ppm. ^{13}C NMR (75.5 MHz, DMSO): δ = 152.7, 135.8, 127.3, 125.1, 124.2, 116.3, 112.4, 112.2, 108.8, 27.2, 26.5, 26.0, 25.1, 21.0 ppm. $C_{14}H_{20}O_5$ (268.31): calcd. C 62.67, H 7.51; found C 62.80, H 7.30.

General Procedure for the Preparation of 12, 18, 20 and 23 (Ozonolysis of Unsaturated Hydroperoxy Compounds 9, 16 and 21): A solution of unsaturated hydroperoxy compound **9**, **16** or **21** (1.5 mmol) in diethyl ether/trifluoroethanol (2:1 v/v, 21 mL) was cooled to 0 °C and ozone (ca. 6 g/h) was bubbled through it for 15 min. Aqueous KH_2PO_4 (10 mL) was added and the mixture was extracted with diethyl ether, washed with brine and dried with Na_2SO_4. After evaporation of the solvent, the crude products were separated by column chromatography on silica gel.

5′-Hydroperoxyspiro[indane-1,3′-[1,2]dioxolane] (12a): Colorless oil (1:1 mixture of two diastereomers); yield 0.22 g (71%), R_f (hexane/EtOAc, 8:2) = 0.31. ^{1}H NMR (300 MHz, DMSO): δ = 9.30 (s, 1 H), 7.11–7.29 (m, 4 H), 5.81–5.94 (m, 1 H), 2.71–3.08 (m, 4 H), 2.26–2.66 (m, 2 H) ppm. ^{13}C NMR (75.5 MHz, DMSO): δ = 146.0, 143.5, 133.4, 129.2, 127.1, 127.0, 125.1, 124.9, 124.2, 123.3, 123.0, 107.9, 93.6, 93.2, 48.4, 48.2, 34.8, 38.7 ppm. $C_{11}H_{12}O_4$ (208.21): calcd. C 63.45, H 5.81; found C 63.38; H 5.62.

6′-Hydroperoxyspiro[indane-1,3′-[1,2]dioxane] (12b): Colorless oil (2:1 mixture of two diastereomers); yield 0.16 g (48%), R_f (hexane/EtOAc, 8:2) = 0.25. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.97, 9.02 (2×s, 1 H), 7.21–7.39 (m, 4 H), 5.57–5.63 (m, 1 H), 2.80–3.21 (m, 3 H), 1.97–2.51 (m, 6 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 143.9, 143.9, 130.0, 129.1, 126.7, 125.1, 125.0, 124.2, 106.3, 104.0, 91.4, 35.8, 34.3, 29.4, 29.1, 26.9, 22.0, 21.8 ppm. $C_{12}H_{14}O_4$ (222.24): calcd. C 64.85, H 6.35; found C 64.66, H 6.50.

5′-Hydroperoxy-1,2,3,4-tetrahydrospiro[naphthalene-1,3′-[1,2]dioxolane] (12c): Colorless oil (1:1 mixture of two diastereomers); yield 70 mg (21%), R_f (hexane/EtOAc, 7:3) = 0.35. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.65 (s, 1 H), 7.53–7.65 (m, 1 H), 7.17–7.25 (m, 2 H), 7.05–7.11 (m, 1 H), 5.85–5.97 (m,1 H), 2.63–2.89 (m, 4 H), 1.71–2.13 (m, 4 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 139.7, 139.5, 136.7, 129.1, 128.8, 128.4, 128.0, 127.8, 126.6, 126.5, 126.4, 108.0, 107.7, 84.5, 84.2, 52.4, 52.2, 35.5, 33.9, 29.7, 29.0, 21.4, 20.0 ppm. HRMS (ESI): calcd. for $C_{12}H_{14}O_4Na$: 245.0784; found 245.0783.

6′-Hydroperoxy-1,2,3,4-tetrahydrospiro[naphthalene-1,3′-[1,2]dioxane] (12d): Colorless oil (2:1 mixture of two diastereomers); yield 92 mg (26%), R_f (hexane/EtOAc, 8:2) = 0.19. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.56 (s, 1 H), 7.09–7.15 (m, 3 H), 6.97–7.03 (m, 1 H), 5.32–5.56 (m, 1 H), 2.66–2.71 (m, 2 H), 1.49–1.99 (m, 8 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 139.7, 139.0, 137.4, 136.8, 128.7, 128.5, 127.8, 127.3, 126.4, 126.3, 107.1, 104.2, 81.9, 80.3, 31.6, 31.5, 30.0, 29.9, 29.8, 29.4, 21.3, 21.2, 19.9, 19.2 ppm. HRMS (ESI): calcd. for $C_{13}H_{16}O_4Na$: 259.0941; found 259.0939.

5′-Hydroperoxyspiro[chromane-2,3′-[1,2]dioxolane] (18a): M.p. 85 °C; yield 60 mg (18%), R_f (hexane/EtOAc, 8:2) = 0.14. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.40 (s, 1 H), 7.06 (t, J = 7.92 Hz, 1 H), 7.00 (d, J = 7.53 Hz, 1 H), 6.84 (dt, J = 1.13, 7.54 Hz, 1 H), 6.80 (d, J = 8.29 Hz, 1 H), 5.89 (dd, J = 1.88, 6.40 Hz, 1 H), 3.11 (dd, J = 6.40, 14.31 Hz, 1 H), 2.78–2.92 (m, 1 H), 2.63–2.74 (m, 1 H), 2.47 (dd, J = 1.88, 14.32 Hz, 1 H), 2.08–2.16 (m, 2 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 152.0, 129.2, 127.8, 121.7, 121.0, 117.4, 107.1, 105.1, 49.7, 27.1, 22.5 ppm. $C_{11}H_{12}O_5$ (224.21): calcd. C 58.93, H 5.39; found C 58.73, H 5.55.

6′-Hydroperoxyspiro[chromane-2,3′-[1,2]dioxane] (18b): Colorless oil; yield 43 mg (12%), R_f (hexane/EtOAc, 8:2) = 0.18. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.97 (s, 1 H), 7.05–7.18 (m, 2 H), 6.90–6.95 (m, 2 H), 5.54 (t, J = 6.03 Hz, 1 H), 2.90 (dt, J = 6.40, 13.57 Hz, 1 H), 2.74 (ddd, J = 1.88, 6.40, 16.57 Hz, 1 H), 2.15–2.34 (m, 2 H), 1.95–2.01 (m, 2 H), 1.82 (dt, J = 6.40, 13.57 Hz, 1 H), 1.54–1.67 (m, 1 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 151.9, 129.1, 127.6, 121.5, 121.4, 117.3, 105.6, 101.3, 28.6, 28.4, 20.7, 20.4 ppm. HRMS (ESI): calcd. for $C_{24}H_{28}O_{10}Na$: 499.1580; found 499.1578.

6′-Hydroxyspiro[chromane-2,3′-[1,2]dioxane] (20b): M.p. 140 °C; yield 57 mg (17%), R_f (hexane/EtOAc, 7:3) = 0.21. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.06 (t, J = 7.54 Hz, 1 H), 6.99 (d, J = 7.54 Hz, 1 H), 6.81–6.88 (m, 2 H), 5.38 (t, J = 4.53 Hz, 1 H), 3.42 (s, 1 H), 2.85 (dt, J = 6.03, 16.55 Hz, 1 H), 2.56 (ddd, J = 1.88, 6.03, 16.58 Hz, 1 H), 2.11–2.32 (m, 2 H), 1.91–1.98 (m, 1 H), 1.57–1.88 (m, 3 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 152.0, 129.1, 127.4, 121.7, 121.2, 117.2, 100.8, 96.4, 28.8, 28.0, 24.3, 20.7 ppm. HRMS (ESI): calcd. for $C_{12}H_{14}O_4$: 222.0892; found 222.0893.

7′-Hydroperoxyspiro[chromane-2,3′-[1,2]dioxepane] (18e): Colorless oil (diastereomeric mixture); yield 0.19 g (49%).

Major Diastereomer: R_f (hexane/EtOAc, 8:2) = 0.34. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.40 (s, 1 H), 7.03 (d, J = 7.53 Hz, 1 H), 6.98 (d, J = 7.53 Hz, 1 H), 6.76–6.85 (m, 2 H), 5.23–5.32 (m, 1 H), 2.85 (dt, J = 5.54, 13.56 Hz, 1 H), 2.41–2.59 (m, 2 H), 2.03–2.15 (m, 1 H), 1.91–2.03 (m, 2 H), 1.64–1.75 (m, 1 H), 1.52–1.64 (m, 3 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 152.0, 129.1, 127.4, 122.2, 121.4, 117.1, 110.8, 105.9, 39.0, 30.3, 27.4, 21.0, 18.1 ppm.

Minor Diastereomer: R_f (hexane/EtOAc, 8:2) = 0.28. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.99 (s, 1 H), 7.04–7.19 (m, 2 H), 6.88–7.00 (m, 2 H), 5.33–5.42 (m, 1 H), 2.83–3.00 (m, 1 H), 2.54–2.68 (m, 1 H), 2.21–2.31 (m, 1 H), 1.98–2.20 (m, 3 H), 1.62–1.89 (m, 4 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 151.7, 129.2, 127.50, 121.6, 121.3, 117.1, 109.8, 104.1, 39.6, 29.7, 29.0, 21.0, 18.1 ppm. HRMS (ESI): calcd. for $C_{13}H_{16}O_5Na$: 275.0895; found 275.0897.

7′-Hydroxyspiro[chromane-2,3′-[1,2]dioxepane] (20e): Colorless oil (1:1 mixture of two diastereomers); yield 38 mg (15%), R_f (hexane/EtOAc, 8:2) = 0.17. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.94–7.09 (m, 4 H), 6.77–6.88 (m, 4 H), 5.14–5.28 (m, 2 H), 3.20–3.49 (m, 2 H), 2.71–2.93 (m, 2 H), 2.48–2.59 (m, 2 H), 2.16–2.34 (m, 3 H) 1.93–2.12 (m, 4 H) 1.76–1.90 (m, 4 H), 1.50–1.75 (m, 5 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 152.1, 151.9, 129.2, 129.0, 127.4, 122.0, 121.7, 121.2, 121.2, 117.3, 117.1, 105.4, 104.3, 102.4, 100.8, 39.6, 38.4, 36.1, 34.8, 29.1, 28.1, 21.1, 18.2, 18.0 ppm.

2-{3-[3,5-Bis(hydroperoxy)-1,2-dioxolan-3-yl]propyl}phenol (23c): Colorless oil; yield 91 mg (22%), R_f (hexane/EtOAc, 1:1) = 0.31. ^{1}H NMR (300 MHz, CD_3CN): δ = 10.28 (s, 1 H), 9.58 (s, 1 H), 6.93–7.02 (m, 2 H), 6.69–6.74 (m, 3 H), 5.57 (dd, J = 1.51, 8.29 Hz, 1 H), 2.51 (t, J = 7.35 Hz, 2 H), 2.28–2.33 (m, 2 H), 1.42–1.72 (m, 4 H) ppm. ^{13}C NMR (75.5 MHz, CD_3CN): δ = 156.2, 131.8, 129.7, 128.7, 121.5, 116.6, 114.2, 108.3, 46.5, 31.3, 31.0, 26.4 ppm. HRMS (ESI): calcd. for $C_{12}H_{16}O_7Na$: 295.0787; found 295.0788.

2-{3-[3,6-Bis(hydroperoxyl)-1,2-dioxan-3-yl]propyl}phenol (23d): Colorless oil; yield 0.12 g (28%), R_f (hexane/EtOAc, 1:1) = 0.28. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.78 (s, 1 H), 9.00 (s, 1 H), 7.04–7.10 (m, 3 H), 6.85 (t, J = 7.35 Hz, 1 H), 5.58 (s, 1 H), 5.44 (t, J = 5.84 Hz, 1 H), 2.54–2.70 (m, 2 H), 1.63–1.95 (m, 8 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 153.4, 130.3, 127.8, 127.4, 120.9, 115.5, 110.8, 105.9, 30.2, 29.8, 23.3, 23.2, 20.3 ppm. HRMS (ESI): calcd. for $C_{13}H_{18}O_7Na$: 309.0945; found 309.0944.

2-(3-Hydroperoxy-3-methoxypropyl)chroman-2-yl Hydroperoxide (24) and 2-[2-(1,2,4-Trioxolan-3-yl)ethyl]chroman-2-yl Hydroperoxide (25): A solution of **16b** (248 mg, 1.13 mmol) in diethyl ether/methanol (1:1 v/v, 30 mL) was cooled to –78 °C and ozone (ca. 6 g/h) was bubbled through it for 15 min. Aqueous KH_2PO_4 (20 mL) was added and the mixture was extracted with diethyl ether, washed with brine and dried with Na_2SO_4. After evaporation of the solvent, the crude products were separated by column chromatography on silica gel.

2-(3-Hydroperoxy-3-methoxypropyl)chroman-2-yl Hydroperoxide (24): Colorless oil; yield 0.21 g (67%), R_f (hexane/EtOAc, 7:3) = 0.23. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.3 (br. s, 1 H), 9.1 (br. s, 1 H), 6.92–7.05 (m, 2 H), 6.75–6.85 (m, 2 H), 4.65–4.74 (m, 1 H), 3.39 (s, 3 H), 2.67–2.84 (m, 1 H), 2.45–2.58 (m, 1 H), 2.00–2.23 (m, 2 H), 1.65–1.96 (m, 4 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 152.0, 129.2, 127.4, 122.0, 121.2, 117.0, 108.2, 104.4, 56.0, 30.3, 26.6, 25.6, 20.9 ppm. HRMS (EI): calcd. for $C_{13}H_{18}O_6$: 270.1103; found 270.1103.

2-[2-(1,2,4-Trioxolan-3-yl)ethyl]chroman-2-yl Hydroperoxide (25): Colorless oil; yield 36 mg (12%), R_f (hexane/EtOAc, 7:3) = 0.47. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (br. s, 1 H), 7.04–7.16 (m, 2 H), 6.86–6.94 (m, 2 H), 5.27 (t, J = 4.52 Hz, 1 H), 5.18 (d, J = 1.89 Hz, 1 H), 5.08 (d, J = 1.51 Hz, 1 H), 2.87 (ddd, J = 6.03, 12.81, 16.58 Hz, 1 H), 2.63 (ddd, J = 3.01, 6.03, 16.58 Hz, 1 H), 2.23–2.34 (m, 1 H), 2.12–2.22 (m, 1 H), 1.79–2.11 (m, 4 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 151.8, 129.2, 127.5, 122.0, 121.4, 117.0, 104.3, 103.2, 94.2, 29.6, 26.7, 25.8, 20.9 ppm. HRMS (EI): calcd. for $C_{13}H_{16}O_6$: 268.0947; found 268.0946.

Supporting Information (for details see the footnote on the first page of this article): Procedures for the synthesis of starting materials **8** including ^{1}H and ^{13}C NMR spectral data.

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