Iron(III) and Copper(II) Catalysed Transformations of Fatty Acid Hydroperoxides: Efficient Generation of Peroxy Radicals with Copper(II) Trifluoromethanesulphonate

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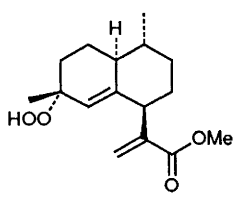
Whereas methyl (9*Z*,11*E*,13*S*)-13-hydroperoxyoctadeca-9,11-dienoate (**3**) and methyl (9*Z*,11*E*,13*S*,15*Z*)-13-hydroperoxyoctadeca-9,11,15-trienoate (**4**) are converted by $FeCl_3$ dietherate into epoxy alcohols and chloroepoxides, catalytic amounts of copper(II) trifluoromethanesulphonate in the presence of octanoic acid under oxygen efficiently convert the second compound into hydroperoxy dioxolanes and dioxabicycloheptanes, and methyl (5*Z*,8*Z*,11*Z*,13*E*,15*S*)-15-hydroperoxyeicosa-5,8,11,13-tetraenoate (15-HPETE methyl ester, **18**) into hydroperoxy bisdioxolanes *via* an 11-peroxy radical.

Peroxy radicals, generated by the autoxidation of unsaturated hydrocarbons and ethers, are important intermediates in a number of processes ranging from biosynthesis to degradation. Homoallylic peroxy radicals have been shown to readily form α-dioxolanyl alkyl radicals that may either react with molecular oxygen[1,2,3] or undergo cyclisation with a diene functionality to give prostaglandin-like structures.[4,5]

As part of an investigation into the reactions of hydroperoxides with transition-metal catalysts we have shown that cyclic allylic hydroperoxides, when treated with Lewis acids such as



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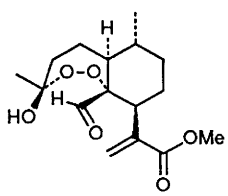

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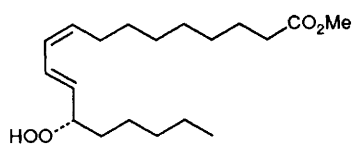

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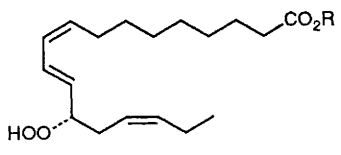
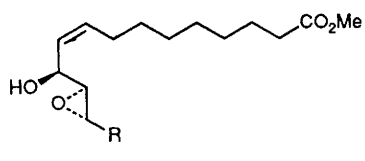
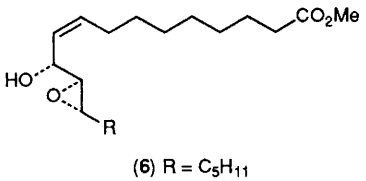


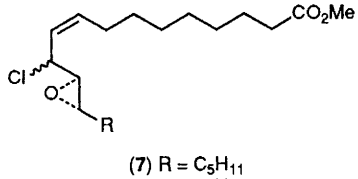
(4) R = Me
(12) R = H



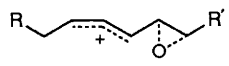
(5) R = C_5H_{11}
(8) R = C_5H_9



(6) R = C_5H_{11}
(9) R = C_5H_9



(7) R = C_5H_{11}
(10) R = C_5H_9



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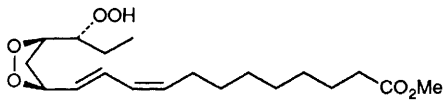

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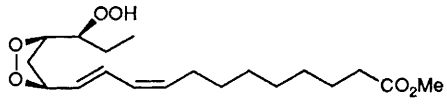

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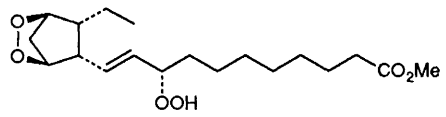

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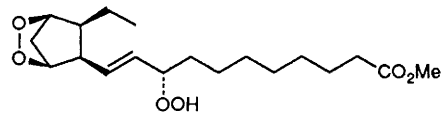

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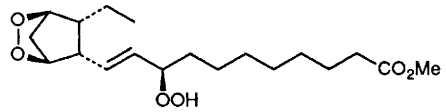

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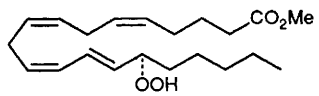

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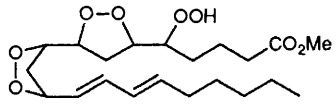

(19)

$FeCl_3$ and the outer-sphere oxidants $Fe(phen)_3(PF_6)_3$ and $Cu(OTf)_2$ (OTf = CF_3SO_3), are cleaved to dicarbonyl compounds.[6] The intramolecular addition of a peroxy radical to the allylic double bond was postulated to take place, in the case of the latter reagents, to give an α-dioxetanyl radical.[6] This was supported by the observation that the allylic hydroperoxide derived from the methyl ester of qinghao acid (**1**) underwent cleavage and concomitant oxygenation in the presence of $Cu(OTf)_2$ to give an aldehydo peroxyhemiacetal (**2**).[7]

We now report that this C–C bond cleavage does not take place with acyclic dienyl and dienyl-homoallylic hydroperoxides derived from unsaturated fatty acids. Treatment of methyl 13-hydroperoxylinoleate [MLH, (**3**), 0.06 M] in dichloromethane (5 ml) under O_2 or N_2 with $FeCl_3$ dietherate (0.2 equiv.) at 0 °C rapidly gave a mixture of epoxy alcohols (**5**) and (**6**) and chloroepoxide (**7**) (stereochemistry undetermined) in the ratio 21 : 30 : 49 (49% overall yield). Methyl 13-hydroperoxylinolenate (MLLH, (**4**), 0.05 M) under the same conditions gave epoxy alcohols (**8**) and (**9**) and chloroepoxide (**10**) (stereochemistry undetermined) in the ratio 24 : 26 : 50 (50% overall yield).[8] The $FeCl_3$ acts as a Lewis acid and facilitates heterolysis of the hydroperoxy group *via* an internal displacement by the *trans* double bond of the diene to give an epoxy allylic carbocation (**11**). This carbocation may rapidly be trapped with a hydroxide ion (iron-bound or from water) or a chloride ion. A related reaction catalysed by protic acid in an aqueous medium has been described elsewhere.[9] That a reaction of this type, rather than the cleavage characteristic of the cyclic allylic hydroperoxides, takes place is attributed to the increased flexibility of the acyclic hydroperoxide allowing a favourable geometry for the heterolytic displacement of hydroxide from the complexed hydroperoxide by the double bond.

In contrast, treatment of MLH (**3**) and MLLH (**4**) with either $Fe(phen)_3(PF_6)_3$ or $Cu(OTf)_2$ or a mixture of the two catalysts did not give products of this type; the reactions proceeded very slowly under both O_2 and N_2 to give predominantly low yields of less polar products which appeared to be dimeric peroxides. However, when the free acid, 13-hydroperoxylinolenic acid [LLH, (**12**), 0.03 M] in MeCN (5 ml) at −20 °C under O_2 was treated with $Cu(OTf)_2$ (0.1 equiv.), it was cleanly converted after 4—5 h into two epimers of the hydroperoxy dioxolane, (**13**) and (**14**),[3]† (33% yield; ratio 42:58, after treatment of the crude product mixture with diazomethane in diethyl ether). Owing to their limited stability the free acid products could not easily be isolated. The use of $Fe(phen)_3(PF_6)_3$ under the same conditions gave no peroxidic products, although a Fe^{III}/Cu^{II} mixed catalyst [0.1 equiv., containing equimolar amounts of $Fe(phen)_3(PF_6)_3$ and $Cu(OTf)_2$] was effective. The differing capacities of $Cu(OTf)_2$ and $Fe(phen)_3(PF_6)_3$ to promote oxygenation of alkyl radicals have been observed in the case of the hydroperoxide of qinghao acid methyl ester (**1**).[7]

When LLH (**12**) (0.02 M) was treated with $Cu(OTf)_2$ (0.1 equiv.) in acetonitrile at 10 °C under oxygen, significant amounts of unstable non-UV-active peroxidic products were obtained together with the hydroperoxy dioxolanes. Attempts to isolate and identify these were unsuccessful due to the instability of the acid products both under the reaction conditions and during isolation. However, treatment of the methyl ester MLLH, (**4**), (78.2 mg, 2.4×10^{-4} mol, 0.06 M) in dichloromethane (4 ml) with an external saturated fatty acid, octanoic acid (0.2 equiv.), followed by $Cu(OTf)_2$ (0.1 M in MeCN, 0.1 equiv.) for 40 min overcame this problem. The hydroperoxy dioxolanes (**13**) and (**14**) (19.6 mg, 23%) and the non-UV-active components (31.9 mg) were isolated by flash chromatography on silica (ethyl acetate–light petroleum, 3:7, 0 °C) and then the non-UV-active fraction was resolved by HPLC (ethyl acetate–light petroleum, 1:3). The latter fraction consisted of the hydroperoxy dioxabicycloheptane stereoisomers (**15**), (**16**), and (**17**) (approximate ratio 14:77:9). The increased selectivity for stereoisomer (**16**) as compared to that previously reported is noteworthy.[4] At −20 °C MLLH (**4**) was converted into the hydroperoxy dioxolanes (**13**) and (**14**) under the above conditions in 63% yield.

Methyl (5*Z*,8*Z*,11*Z*,13*E*,15*S*)-15-hydroperoxyeicosa-5,8,11,13-tetraenoate (15-HPETE methyl ester, **18**) (0.03 M) in dichloromethane (12 ml) containing octanoic acid (0.2 equiv.) was similarly treated with $Cu(OTf)_2$ (0.1 M in MeCN, 0.1 equiv.) at 5 °C for 16 h in a sealed reaction vessel purged with O_2. Several isomers of the hydroperoxy bisdioxolanes (**19**) were obtained in 44% yield together with unchanged starting material. The isomers were separated by HPLC (Whatman Partisil 10 M20, 22 × 500 mm, ethyl acetate–light petroleum, 1:4) into six major components with R_T: (i) 59, (ii); 64, (iii) 71, (iv) 76, (v) 103, (vi) 125 min, in a ratio of 22:22:11:11:23:11.‡ Such products arise as a result of a facile rearrangement of the 15-peroxy radical to the 11-peroxy radical and subsequent cyclisation of the latter in the presence of O_2, as has been reported by Porter.[10]

While the above results correspond very closely to those achieved by other workers with traditional radical initiators such as t-butyl peroxyoxalate or t-butyl hyponitrite, the new system described here increases the rate of the reaction and substantially increases the product yields. This is attributed to the rapid generation of peroxy radicals, and to the greater selectivity of the $Cu(OTf)_2$, as allylic abstraction does not occur with this catalyst. For these reasons, the use of the catalyst permits thermally unstable products such as those related to prostaglandin endoperoxides to be isolated quickly and with relative ease. Nevertheless, while prostaglandin-like structures have been successfully obtained by us and previous workers, these have consistently been formed with the unnatural *cis*-configuration of the side chains.[4,5] This intriguing and exclusive stereochemical bias calls into question the currently accepted mechanism by which arachidonic acid is enzymatically transformed into prostaglandin G_2 (PGG_2).[4,5,11] Specifically, the premise that the carbocyclisation step proceeds *via* a free radical mechanism needs to be examined further.[12]

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† Stereochemical assignments based on ref. 1.

‡ *Selected NMR data* for fraction 2: ^1H (200 MHz, $CDCl_3$) δ 0.89 (3H, t, $J_{20,19}$ 6.2 Hz, H-20), 1.16—2.46 (15H, m, H-2, -3, -4, 1 × H-7, H-16, -17, -18, -19), 2.61—2.99 (3H, m, 1 × H-7, 2 × H-10), 3.69 (3H, s, CO_2Me), 4.04 (1H, dt, $J_{5,6}$ 7.4, $J_{5,4}$ 5.1 Hz, H-5), 4.30—4.51 (3H, m, H-6, -8, -9); 4.71 (1H, ddd, $J_{11,10\alpha} = J_{11,10\beta} = J_{11,12}$ 7.6 Hz, H-11), 5.44 (1H, dd, $J_{12,13}$ 15.2, $J_{12,11}$ 8 Hz, H-12), 5.78 (1H, dt, $J_{15,14}$ 15.2, $J_{15,16}$ 6.9 Hz, H-15), 6.04 [1H, dd, $J_{14,15}$ 15.2, $J_{14,13}$ 10.3 Hz, H-14(13)], 6.31 [1H, dd, $J_{13,12}$ 15.2, $J_{13,14}$ 10.3 Hz, H-13(14)]; ^{13}C (50 MHz, $CDCl_3$) δ 174.46 (CO_2Me), 138.04, 136.89, 128.77, 123.69, 84.05, 82.69, 82.50, 82.12, 81.05, 51.76 (CO_2Me), 44.27, 38.66, 33.34, 32.57, 31.34, 28.68, 28.46, 22.48, 20.55, 14.00 (C-20).

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12 A specific model accounting for the unnatural *cis*-cyclisation of the immediate radical precursor of the dioxabicycloheptane nucleus of PGG_2 has been put forward by Corey (ref. 5). Hex-5-enyl radicals, in the absence of another functionality, undergo predominant *cis*-cyclisation, and so stabilization of the radical through orbital overlap with the adjacent peroxide oxygen atom and the diene as encapsulated in the model is not an over-riding factor in determining the stereochemical outcome of the cyclisation. See: D. C. Spellmeyer and K. N. Houk, *J. Org. Chem.*, 1987, **52**, 959.