Iron(II)-mediated fragmentation of unsaturated hydroperoxy acetals: a rapid synthetic route to 13-membered macrolides

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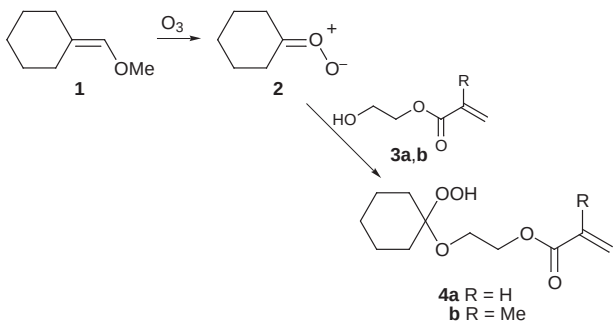
Treatment of (1-hydroperoxy)cyclohexyloxyethyl acrylate with either iron(II) sulfate or iron(II) sulfate/copper(II) chloride affords novel 13-membered macrolides *via* tandem radical scission-cyclisation reactions.

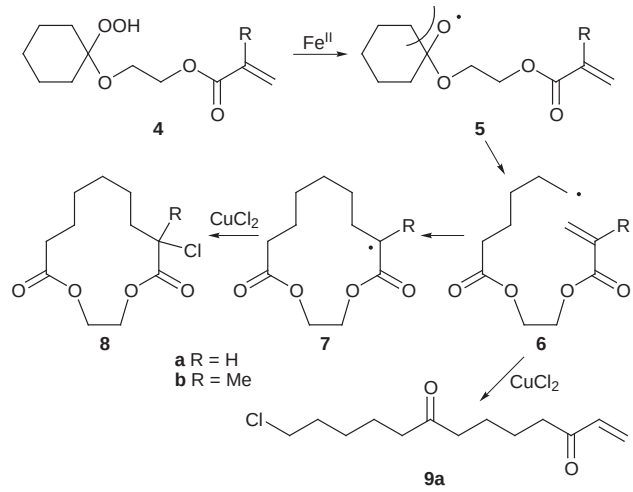
The development of synthetic strategies to macrocyclic compounds has attracted considerable attention because many of them are naturally occurring and several possess important biological properties.[1,2] In this respect, intramolecular radical addition to α,β-unsaturated ketones has been found to provide convenient access to a variety of macrocycles.[3] This method is generally based on the intramolecular cyclisation of the long-chain unsaturated radicals generated by the reaction of the corresponding iodo enones and their homologues with tributyltin hydride.[4] We report herein that the iron(II)-mediated fragmentation of the readily prepared 1-(hydroperoxy)-cycloalkyloxyethyl acrylates provides an alternative approach to the synthesis of novel macrolides.[5,6]

The key to our approach is the ease of preparation of the desired intermediate unsaturated hydroperoxy acetals **4**. Thus, treatment of a solution of vinyl ether **1** and unsaturated alcohol **3** (3 equiv.) in CH_2Cl_2 with ozone (1 equiv.) at −70 °C resulted in the selective ozonolysis of the electron rich vinyl ether **1** to give carbonyl oxide **2** which was subsequently captured by **3** affording the corresponding hydroperoxide **4** in moderate yield (**3a**, 27%; **3b**, 40%) (Scheme 1).[7] Subsequent treatment of a solution of the hydroperoxide **4a** in MeCN with a solution of iron(II) sulfate (1 equiv.) and copper(II) chloride (3 equiv.) in water at room temperature gave the macrolide **8a** (49%) and the acyclic diketone **9a** (17%) (Scheme 2).‡ Compound **8a** was shown to be the structurally novel 13-membered bislactone by X-ray crystallographic analysis (Fig. 1).§ From hydroperoxide **3b**, the corresponding chloro-substituted macrolide **8b** was obtained in 35% yield, along with the unidentified acyclic products.¶

These results indicate that the acyclic radical **6**, generated by sequential fragmentation of the O–O bond to give oxy radical **5** followed by β-scission of the cyclohexylidene ring, had undergone a very efficient intramolecular cyclisation to give **7**, which in turn reacted with copper(II) chloride to provide the chlorinated macrolide **8**.[8]



Scheme 1



Scheme 2

In the absence of copper(II) chloride, the reaction of the hydroperoxide **4a** with iron(II) sulfate (2 equiv.) yielded three new crystalline products: the monomeric bislactone **10a** (18%) and two dimeric isomers **11a** (Scheme 3). X-Ray crystallographic analysis of the higher melting dimer (mp 168 °C; 25%) demonstrated unambiguously that this was the *meso*-isomer (Fig. 2).‖ Thus, the other dimeric isomer **11a** (mp 140.5–141.5 °C; 25%) was assigned as the *dl* form. From the hydroperoxide **4b**, the monocyclic macrolide **10b** was obtained in 25% yield along with unidentified acyclic products. Since the corresponding dimeric compounds were not observed in significant quantities, it appears that the sterically more hindered radical **7b** does not undergo dimerisation as readily as **7a**.

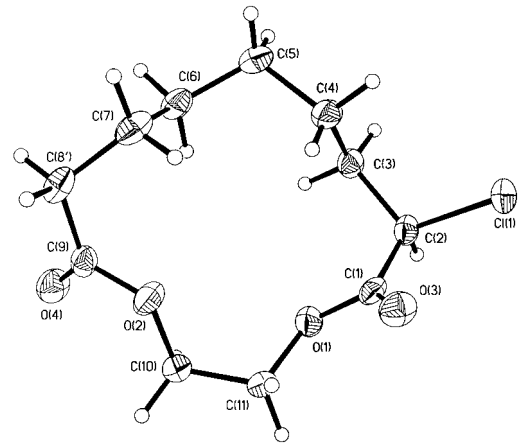
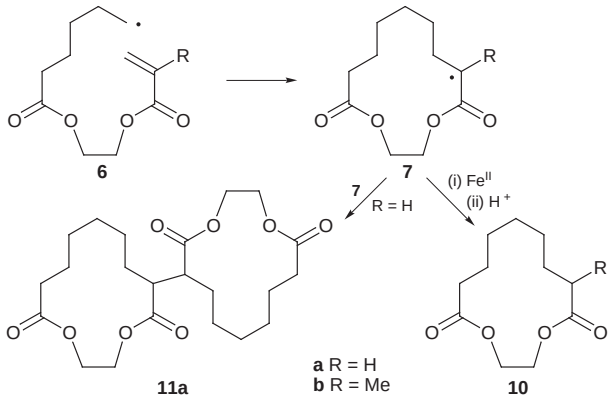


Fig. 1 The molecular structure of macrolide **8a** as determined by X-ray crystallography (ORTEP, 50% probability ellipsoids for non-hydrogen atoms) (ref. 10)



Scheme 3

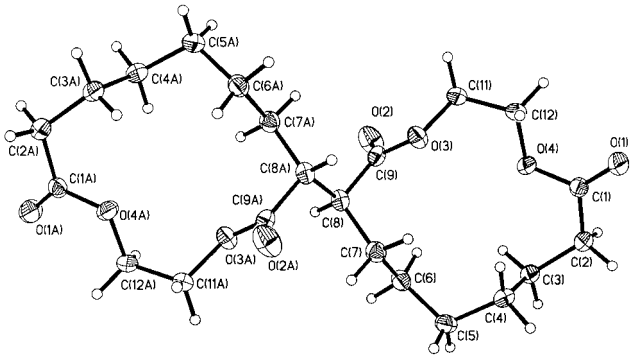
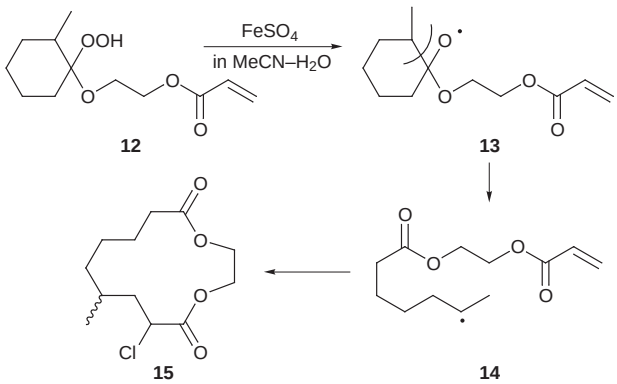


Fig. 2 The molecular structure of the dimeric macrolide **11a** as determined by X-ray crystallography (ORTEP, 50% probability ellipsoids for non-hydrogen atoms) (ref. 10)

The iron(II) catalysed decomposition of the methyl-substituted hydroperoxide **12** results in the formation of the monomeric chloromacrolide **15** as the sole isolable product (54%, a mixture of two isomers in the ratio *ca*. 2 : 1). Thus, intermediate **13** had undergone a selective β-scission of the cyclohexylidene ring *via* the more highly substituted radical **14** as outlined in Scheme 4. Similar selectivity has been observed previously in the thermal rearrangements of α-substituted 1,2,4-trioxanes.[9]

In summary, the readily available unsaturated hydroperoxy acetals such as **4** offer considerable potential as precursors of novel macrolides. The fragmentation-cyclisation reactions take place under relatively mild conditions and do not require high



Scheme 4

dilution techniques (0.01–0.05 M). Moreover, the mode of termination can be controlled by the judicious choice of reaction conditions.

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Notes and References

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‡ All new compounds gave satisfactory microanalytical and spectroscopic data.

§ *Crystal data* for **8a**: $C_{11}H_{17}ClO_4$, M = 248.70, colourless needles, monoclinic, space group $P2_1/c$ (No. 14), a = 15.1404 (12), b = 5.0426 (4), c = 16.1490 (11) Å, β = 100.550 (5)°, U = 1212.12 (2) Å^3, Z = 4, D_c = 1.363 g cm^{-3}, $F(000)$ = 528, μ(Mo-Kα) = 0.312 cm^{-1}. The intensity data were collected on a Siemens P4 diffractometer at 160 (2) K using graphite monochromated Mo-Kα radiation (λ = 0.710693 Å). The structure was solved by direct methods and refined by full-matrix least-squares methods on F^2 using anisotropic temperature factors for the non-hydrogen atoms (SHELXTL[10]). At convergence, the discrepancy indices R_1 and wR_2 were 0.032 [for 1942 data with $F_o > 4\sigma(F_o)$] and 0.0878 (all 2111 unique data) respectively. The final difference Fourier map contained no feature greater than ±0.31 e Å^{-3}.

¶ Since the separation of **8b** from other acyclic products was difficult, the reaction mixture was ozonised further to break down the latter. Thus, **8b** could be cleanly isolated by column chromatography on silica gel.

‖ *Crystal data* for **11a** (higher mp dimer): $C_{22}H_{34}O_8$, M = 426.49, colourless prisms, triclinic, space group $P\bar{1}$ (No. 2), a = 5.0600 (10), b = 8.512 (2), c = 13.090 (2) Å, α = 88.800 (10), β = 83.78 (2), γ = 77.010 (10)°, U = 546.1 (2) Å^3, Z = 1 (molecule on an inversion centre), T = 160(2) K, D_c = 1.297 g cm^{-3}, $F(000)$ = 230, μ(Mo-Kα) = 0.098 cm^{-1}. The final discrepancy indices R_1 and wR_2 were 0.0341 [for 1595 data with $F_o > 4\sigma(F_o)$] and 0.0883 (all 1907 unique data) respectively. The final difference Fourier map contained no feature greater than ±0.20 e Å^{-3}. CCDC 182/842.

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