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

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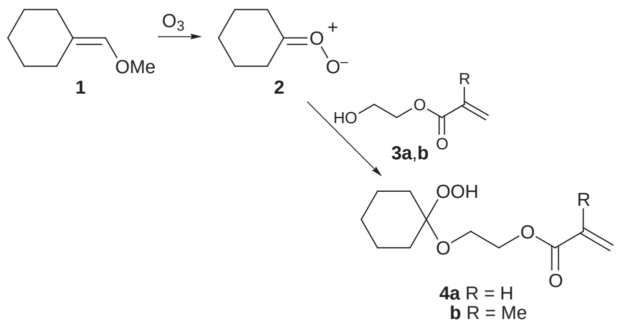
Treatment of (1-hydroperoxy)cyclohexyloxyethyl acrylate with either iron(II) sulfate or iron(II) sulfate/copper(II) chloride affords novel 13-membered macrolides *via* tandem radical scission-cyclisation reactions.

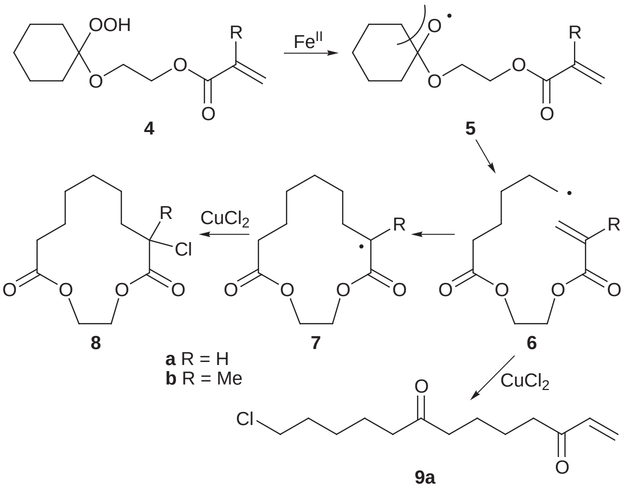
The development of synthetic strategies to macrocyclic compounds has attracted considerable attention because many of them are naturally occurring and several possess important biological properties.[1,2] In this respect, intramolecular radical addition to α,β-unsaturated ketones has been found to provide 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**.

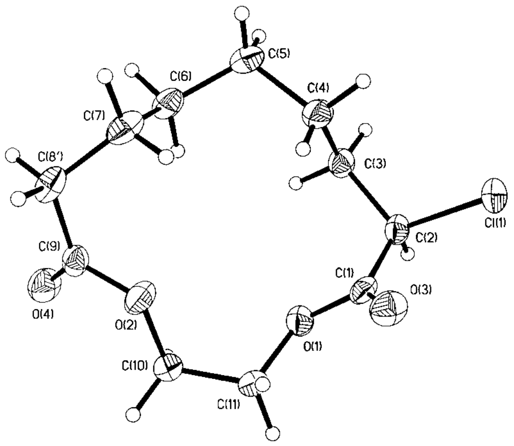
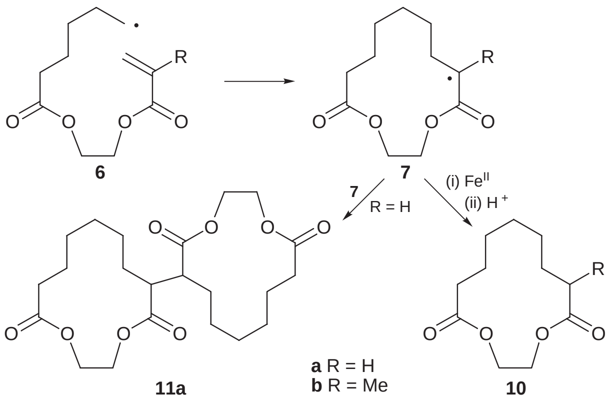


Fig. 1 The molecular structure of macrolide **8a** as determined by X-ray crystallography (ORTEP, 50% probability ellipsoids for non-hydrogen atoms) (ref. 10)



Scheme 3

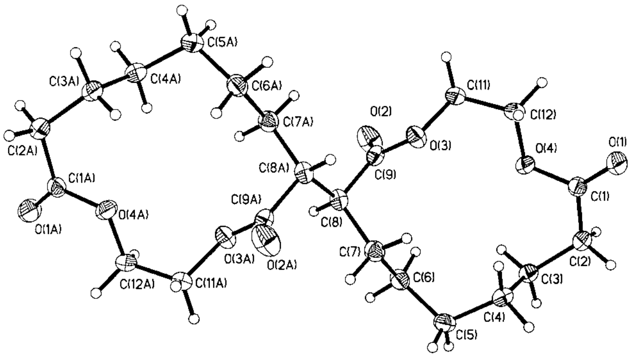
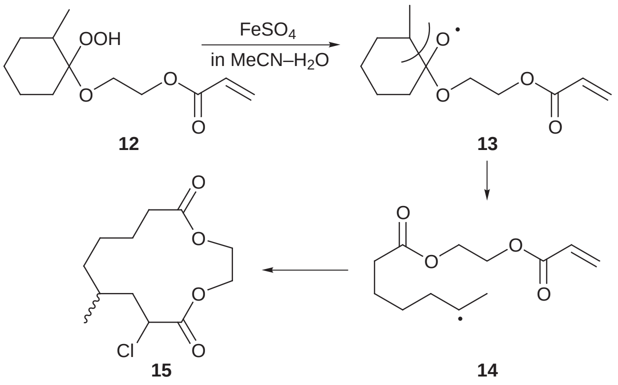


Fig. 2 The molecular structure of the dimeric macrolide **11a** as determined by X-ray crystallography (ORTEP, 50% probability ellipsoids for non-hydrogen atoms) (ref. 10)

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



Scheme 4

This work was supported in part by a Grant-in Aid for Scientific Research on Priority Areas (09270212) from the Ministry of Education, Science, Culture and Sports of Japan. We thank the British Council (Tokyo) for the award of travel grant to K. J. McC., M. N. and A. M.

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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Received in Liverpool, UK, 4th March 1998; 8/01802B