Direct Remote Oxidation of Macrocyclic Lactones

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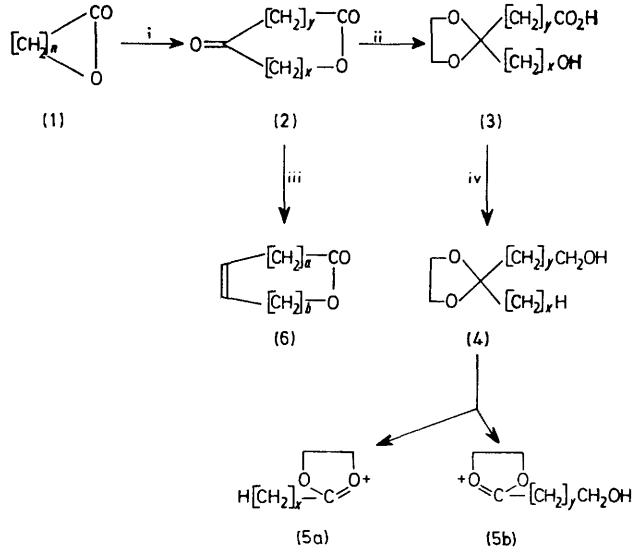
Summary Direct remote oxidation of macrocyclic lactones to a mixture of monoketo-lactones can be accomplished with partial regiospecificity.

THE macrolide antibiotics[1] may be regarded as functional derivatives of undecanolide, tridecanolide, hexadecanolide,



SCHEME. Reagents: i, CrO_3–Ac_2O, HOAc; ii, a, $HOCH_2CH_2OH$, *p*-$MeC_6H_4SO_3H$; b, KOH–MeOH; c, NH_4Cl; iii, a, $NaBH_4$; b, $MeSO_2Cl$, C_5H_5N; c, collidine, heat; iv, a, $MeSO_2Cl$, C_5H_5N; b, $LiAlH_4$.

and heptadecanolide. Indeed it is possible that macrolide biosynthesis involves the intermediacy of saturated lactones of this type and that the introduction of double bonds and oxygen functionality occurs late in the biosynthetic sequence.† In connection with this biosynthetic idea and as an extension of our studies[3] on remote oxidation we

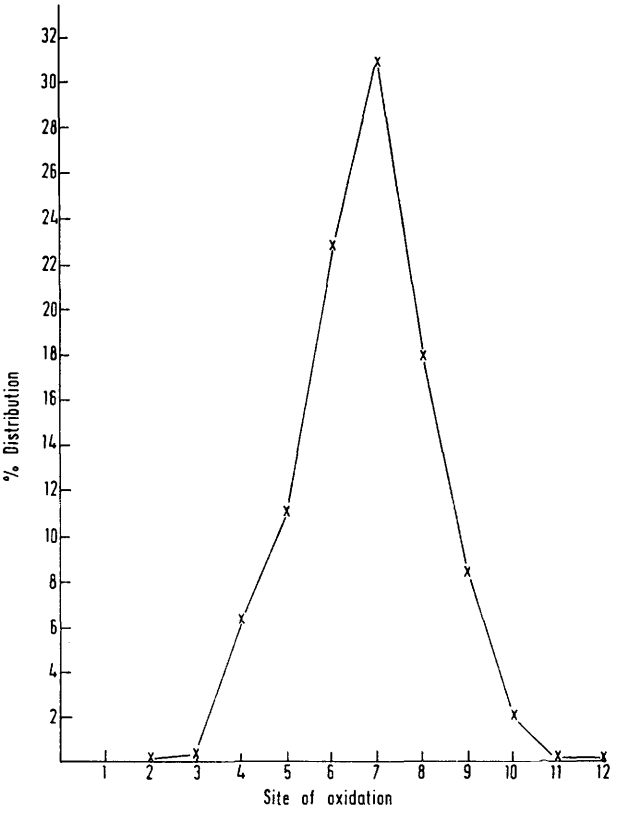


FIGURE 1. Distribution of isomers in oxidation of dodecanolide (**1**; $n = 11$).

† The most generally accepted view of macrolide biosynthesis involves the intermediacy of a propionate-acetate derived β-polyketo-ester which can be partially reduced and lactonised to provide the natural compound.

examined the oxidative vulnerability of various macrocyclic lactones. Treatment of the lactones (**1**; n = 11, 14, or 15) in acetic anhydride–acetic acid with chromium trioxide–acetic anhydride at room temperature for 48 h provided a mixture of the monoketo-lactones (**2**; $x + y$ = 10, 13, or 14) which were separated from starting material by column chromatography. The yield of product based on recovered starting material was 35—40% and the relative amount of isomeric monoketo-lactones‡ was deduced from the mass spectra§ of the derived hydroxy-acetals (**4**; $x + y$ = 10, 13, or 14)[3] (*cf.* Scheme) [fragment ions (**5a**) and (**5b**)].

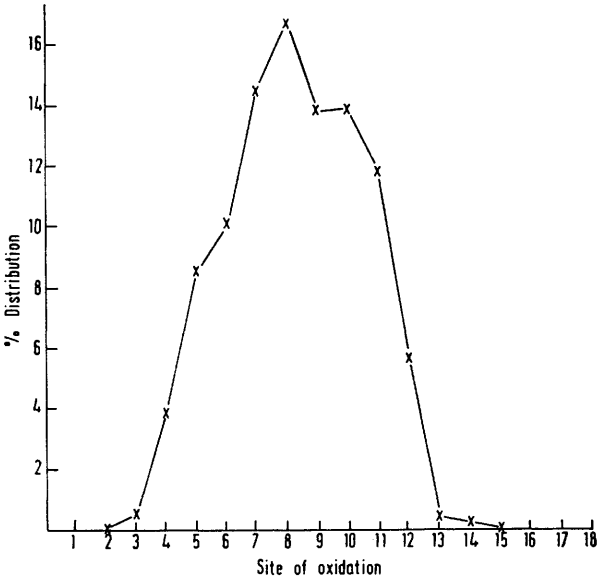


FIGURE 2. Distribution of isomers in oxidation of pentadecanolide (**1**; n = 14).

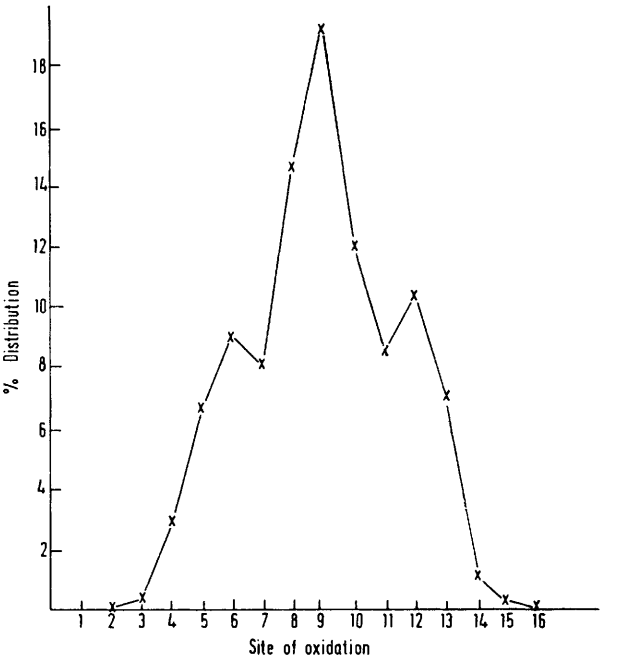


FIGURE 3. Distribution of isomers in oxidation of hexadecanolide (**1**; n = 14).

The results obtained are displayed graphically in Figures 1—3 [low resolution (15 eV); probe 75 °C] and clearly indicate that direct remote oxidation of the macrocyclic lactones occurs with a reasonably high degree of regiospecificity. One possible explanation for the overall results is that complex formation between the lactone group and the oxidising agent coupled with the preferred conformation(s) of the macrocyclic structure could impose severe limitations on possible reactions sites.

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‡ Reduction and dehydration of the pure monoketo-lactone mixture (**2**; $x + y$ = 14) derived from hexadecanolide (**1**; n = 15) provides a mixture of ambrettolide (**6**; a = 5, b = 8) and its positional isomers (*cf.* B. D. Mookherjee, R. W. Trenkle, and R. R. Patel, *J. Org. Chem.*, 1972, **37**, 3846). This mixture is currently being evaluated as an insect sex attractant.

§ Low and high resolution mass spectra at 15 and 70 eV were recorded on Atlas CH-4 and A.E.I. MS 902 instruments. The validity of the mass spectroscopic method for estimating the qualitative and quantitative composition of the product mixture was tested by using known mixtures of ethylene acetals derived from synthetic 9-, 10-, 11-, and 15-oxo-octadecan-1-ol.

[1] Reviews: W. Keller-Schierlein, *Fortschr. Chem. Org. Naturstoffe*, 1973, **30**, 313; W. D. Celmer, *Pure Appl. Chem.*, 1971, **28**, 413; M. Barry, *Quart. Rev.*, 1963, **17**, 343.
[2] C. R. Eck, D. J. Hunter, and T. Money, *J.C.S. Chem. Comm.*, 1974, 865.
[3] R. Breslow, *Chem. Soc. Rev.*, 1972, **1**, 553, and references cited therein.