Synthetic Organic Photochemistry: Macrolides from the Photolysis of βγ-Epoxy-ketones

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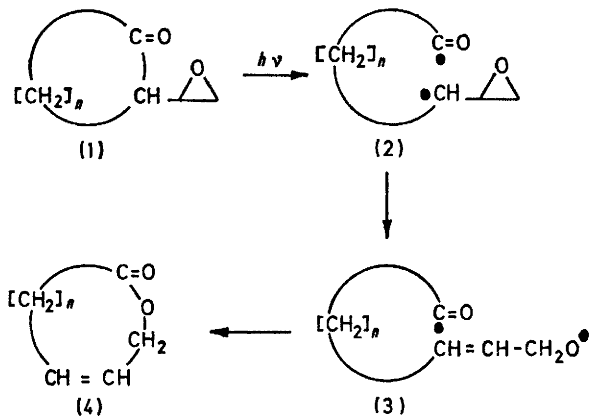
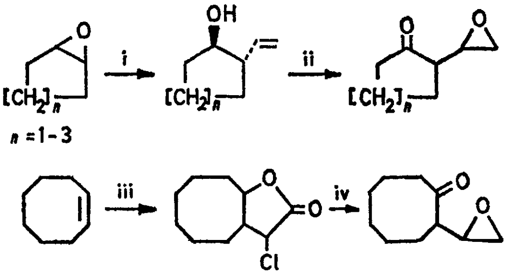
Summary The photolysis of 2-(oxiranyl)cycloalkanones is shown to be a useful method for the synthesis of unsaturated macrolides by a three-atom photochemical ring expansion.

Only limited methods are available for the synthesis of the important class of compounds known as the macrolides. On the basis of our previous work,[1] we have examined the hypothesis that 2-(oxiranyl)cycloalkanones (**1**), like their cyclopropyl counterparts,[1c] would undergo a photochemical ring expansion *via* the sequence (**1**) → (**4**).[2] We now report that such a sequence does indeed occur and that this method provides a useful method for the preparation of macrolides.



Scheme 1

The required epoxy-ketones were prepared from the corresponding cycloalkene oxides as shown in Scheme 2. Because attempts to open cyclo-octene oxide with lithium acetylide, vinyl-lithium, or lithium divinylcopper(I) were unsuccessful the alternative route beginning with the addition of dichloroketen to cyclo-octene was used to prepare the cyclo-octanone derivative. The epoxy-ketones, obtained as mixtures of diastereoisomers, are relatively unstable and quite sensitive to acid and base.



Scheme 2

Reagents: i; a, LiC≡CH–ethylenediamine–Me$_2$SO; b, Na–liq. NH$_3$, (NH$_4$)$_2$SO$_4$; ii; a, *m*-ClC$_6$H$_4$·CO$_3$H; b, CrO$_3$·2py, CH$_2$Cl$_2$; iii; a, Cl$_2$CHCOCl, Et$_3$N; b, Zn–HOAc, Et$_2$O; c, H$_2$O$_2$, HOAc; iv; a, NaBH$_4$; b, NaOMe; c, CrO$_3$·2py, CH$_2$Cl$_2$.

Photolysis† of a 1% hexane solution of a mixture of the two diastereoisomeric 2-(oxiranyl)cyclopentanones (**5**)‡ until approximately 71% of the starting material had been consumed§ gave three products (*ca.* 50% yield) which were separated by column chromatography (silica gel–AgNO$_3$) and were characterized as *Z*-hept-5-enolide (**6**) [65%, ν_{max} 1760, 1640, and 690 cm^{-1}; δ 5·45 (2H, m) and 4·60 (2H,

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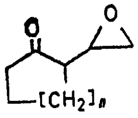
† Photolyses were conducted under nitrogen in a Vycor vessel mounted in the centre of a Rayonet Photochemical Reactor equipped with RPR-3000 Å lamps. All photolyses were followed by g.l.c. and cyclodecane or cyclo-octane was used as an internal standard.

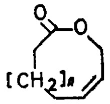
‡ All new compounds gave satisfactory analytical results and/or high-resolution mass spectral data. All spectral data were in accord with the assigned structures and n.m.r. spectra were simplified by decoupling experiments.

§ The reaction was stopped at this point because further irradiation led to the loss of aldehydic product. When the ring-expanded lactones are the desired products the reaction can be extended and higher yields of the ring-expanded products obtained.

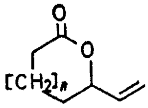
d, *J* 1·8 Hz)], 5-vinylpentanolide (**7**) [25%, ν_{max} 1750, 9·08 and 930 cm^{-1}; δ 5·00—6·00 (3H, m) and 4·75 (1H, m)], and *E*-hept-2-enedial (**8**) [8%, ν_{max} 2740, 1735, 1700, 1645, and 970 cm^{-1}; δ 9·20 (1H, t, *J* 1·5 Hz), 8·90 (1H, d, *J* 8 Hz), 6·20 (1H, d of t, *J* 7 and 16 Hz), and 5·50 (1H, d of d, *J* 8 and 16 Hz)]. Catalytic hydrogenation of (**6**) produced heptanolide and n-heptanoic acid, both of which were identical with authentic samples. Catalytic hydrogenation of (**7**) gave a mixture of n-heptanoic acid and 5-ethylpentanolide identical with an authentic sample prepared by Baeyer–Villiger oxidation of 2-ethylcyclopentanone.



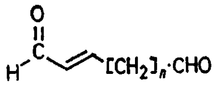
(5) n = 1
(9) n = 2
(13) n = 3
(17) n = 4



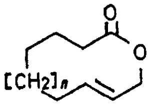
(6) n = 1
(10) n = 2
(14) n = 3
(18) n = 4



(7) n = 1
(11) n = 2



(8) n = 3
(12) n = 4
(16) n = 5
(20) n = 6



(15) n = 1
(19) n = 2

$$(5) \xrightarrow{h\nu} (6) + (7) + (8) \qquad (1)$$

$$(9) \xrightarrow{h\nu} \underset{(ca.\ 52\%)}{(\mathbf{10}} + \underset{(ca.\ 25\%)}{(\mathbf{11})} + \underset{(ca.\ 24\%)}{(\mathbf{12})} \quad (ca.\ 50\%\ \text{overall}) \qquad (2)$$

$$(\mathbf{13}) \xrightarrow{h\nu} \underset{(ca.\ 42\%)}{(\mathbf{14})} + \underset{(ca.\ 26\%)}{(\mathbf{15})} + \underset{(ca.\ 19\%)}{(\mathbf{16})} \quad (ca.\ 50\%\ \text{overall}) \qquad (3)$$

$$(\mathbf{17}) \xrightarrow{h\nu} \underset{(ca.\ 50\%)}{(\mathbf{18})} + \underset{(ca.\ 36\%)}{(\mathbf{19})} + \underset{(ca.\ 7\%)}{(\mathbf{20})} \quad (ca.\ 50\%\ \text{overall}) \qquad (4)$$

Similar photolyses of epoxy-ketones (**9**), (**13**), and (**17**) gave the products indicated in equations (1)—(4). In each case the photoproducts were obtained in *ca.* 50% yield and their relative composition was based upon g.l.c. analysis of the crude photoproduct. The products were characterized as before.

In all the photolyses of the epoxy-ketones the major ring-expanded product arises by the pathway in Scheme 1 and the method is most useful for ring expansions to the ten- and eleven-membered ring systems. As in the ring expansion of the cyclopropyl ketones[1c] the *E*- and *Z*-isomers are photochemically interconverted. The formation of the anomalous one-atom photochemical ring expansion products (**7**) and (**11**) was unexpected and it is not yet clear how they are formed. It may, however, be significant that none of the anomalous products are obtained in the photolysis of (**13**) and (**17**) but that the *E*-lactones are obtained in these cases. This suggests that either the *E*-diradical arising from (**5**) and (**9**) is diverted to other products (*e.g.*, enedial or anomalous product) or that the *E*-lactone is thermally unstable and undergoes an oxy-Cope rearrangement to give (**7**) and (**11**).

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[1] (a) R. G. Carlson and J. H. Bateman, *Tetrahedron Letters*, 1967, 4151; (b) R. G. Carlson and D. E. Henton, *Chem. Comm.*, 1969, 674; (c) R. G. Carlson and E. L. Biersmith, *ibid.*, p. 1049.

[2] The ring opening of radicals α to an oxiran ring is well documented: (a) E. S. Huyser and L. R. Munson, *J. Org. Chem.*, 1965, **30**, 1436; (b) S. K. Pradhan and V. M. Girijavallabhan, *Tetrahedron Letters*, 1968, 3103; (c) E. L. Stogryn and M. H. Gianni, *ibid.*, 1970, 3025.