Preference for 6-*Exo-Trigonal* Closures of ω-Hydroxy-αβ-unsaturated Esters

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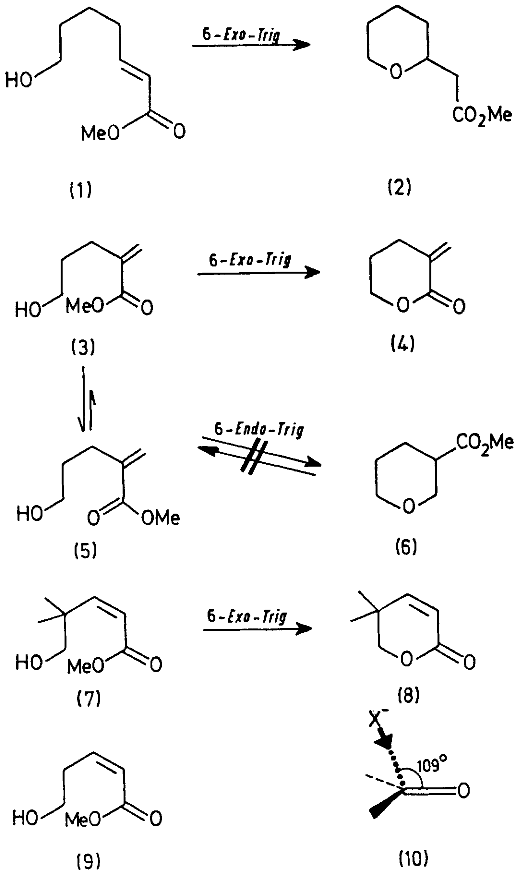
Summary Methyl 5-hydroxy-2-methylenevalerate (**3**) under basic conditions cyclises preferentially to α-methylene-δ-valerolactone (**4**) by a 6-*Exo-Trig* process which is a faster reaction than the alternative 6-*Endo-Trig* mode of ring closure.

In a recent general treatment of ring closure reactions[1] it was suggested that both 6-*Exo-Trigonal* and 6-*Endo-Trigonal* processes are favoured for the formation of six-membered rings. Experimental support for this suggestion was obtained.[2] We now demonstrate that when a choice of these two modes of ring closure exists in ω-hydroxy-αβ-unsaturated esters, the *Exo* pathway is the faster ring closing process.

Treatment of the *trans*-heptenoate ester (**1**)[3] with a variety of bases, *e.g.*, sodium hydride, sodium methoxide, and potassium t-butoxide, led rapidly to the cyclic ether (**2**)[4] in quantitative yield *via* the 6-*Exo-Trig* pathway. In contrast, the ester (**3**)† cyclised relatively slowly under the same conditions to the α-methylene lactone (**4**)[5] and gave none of the product of the 6-*Endo-Trig* mode (*i.e.*, the intramolecular Michael addition) namely, the tetrahydropyran (**6**).[6] The tetrahydropyran (**6**), synthesized by an independent method, was found readily to exchange the proton α to the methoxycarbonyl group under the cyclisation conditions of (**3**) to (**4**), thereby demonstrating that formation of (**4**) is kinetically determined.‡ The approximate relative rates of the ring closures (**1**) → (**2**) and (**3**) → (**4**) are 100—1000 : 1, depending on the basic conditions used. We attribute the relatively slower formation of (**4**) from (**3**) to the preferred *s-trans* conformation (**5**)[7] in which the 6-*Exo-Trig* closure is sterically improbable. In keeping with this explanation is the extremely rapid closure of the ester (**7**)§ to the lactone (**8**)[8] even under neutral conditions.¶

We have previously indicated[1] that the relative facility of the *Exo* over the *Endo* modes of ring closure in the trigonal systems is a result of the trajectory (**10**) for nucleophilic attack on a carbonyl or its analogue.[9]



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† Satisfactory elemental analysis and spectral data were obtained.

‡ It should be remembered that the 6-*Endo-Trig* process is favoured (ref. 1) and such *retro*-6-*Endo-Trig* reactions are known. However, under these reaction conditions the rates of these processes are low relative to the *Exo* mode of ring closure.

§ The ester could not be isolated as a pure single compound. During isolation, rapid formation of the lactone (**8**) occurred.

¶ The dimethyl substituted hydroxy ester (**7**) was chosen for this study rather than the parent hydroxy ester (**9**) in order to prevent the possibility of dehydration (J. W. Cornforth, R. H. Cornforth, G. Popjak, and I. Y. Gore, *Biochem. J.*, 1958, **69**, **146**) occurring as a competing reaction to give a penta-2,4-dienoic acid ester. We realize that the methyl groups probably contribute to the rapid rate of ring closure of the hydroxy ester (**7**) (R. M. Beesley, C. K. Ingold, and J. F. Thorpe, *J. Chem. Soc.*, 1915, **107**, 1080).

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[6] Smith, Kline and French Laboratories, B.P. 1,099,209 (*Chem. Abs.*, 1968, **69**, P10361g).

[7] 1,3-Dienes and αβ-unsaturated aldehydes and ketones are known to have a preferred *s-trans* conformation, see E. Eliel, 'Stereochemistry of Carbon Compounds,' McGraw-Hill, New York, 1962, p. 331. The stereochemistry of αβ-unsaturated esters is less clear and is solvent dependent but the *s-trans* conformation appears to be preferred: D. B. Cunliffe-Jones, *Spectrochim. Acta*, 1965, **21**, 245; R. J. W. LeFevre and K. M. S. Sundaram, *J. Chem. Soc.*, 1963, 1880; 3188.

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[9] For example see: H. B. Burgi, J. D. Dunitz, J.-M. Lehn, and G. Wipff, *Tetrahedron*, 1974, **30**, 1563; H. B. Burgi, J. D. Dunitz, and E. Shefter, *J. Amer. Chem. Soc.*, 1973, **95**, 5065.