# Rules for Ring Closure. Stereoelectronic Control in the Endocyclic Alkylation of Ketone Enolates

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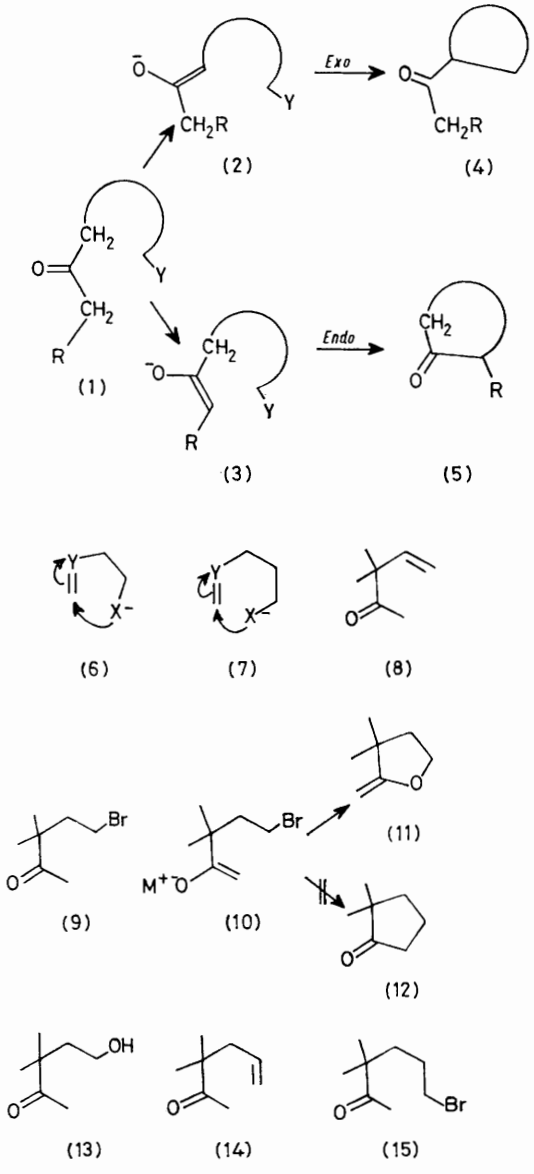
*Summary* Endocyclic alkylation of ketone enolates is shown to depend critically upon the size of the so formed ring and six- but not five-membered cyclic ketones can be synthesized in this way; a rationale for this difference is presented.

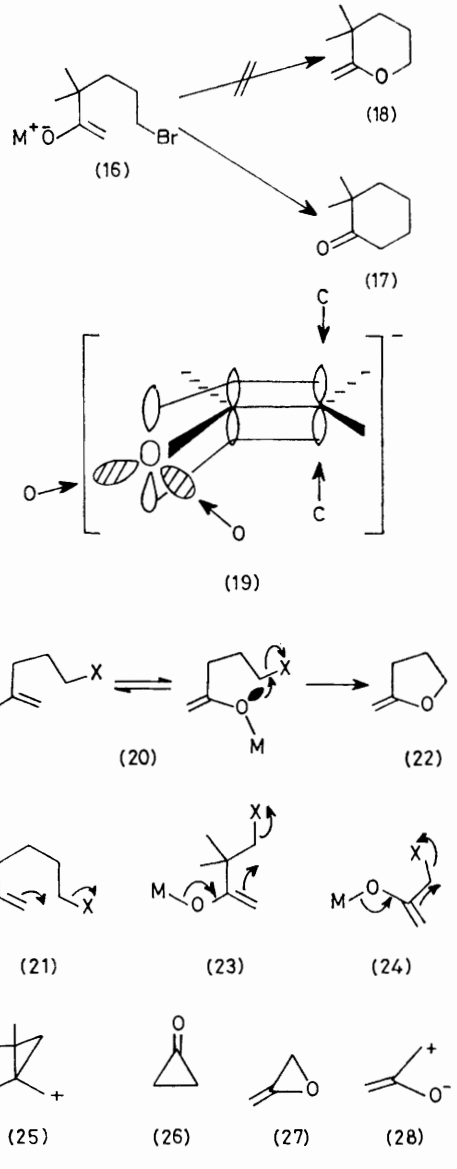
KETONIC substances of the general type (**1**) can be deprotonated to the isomeric enolates (**2**) or (**3**) which, in principle, may be intramolecularly alkylated (when Y is a leaving group) to the ring structures (**4**) or (**5**). Since these alkylations proceed by breakage of the enolate double bond in either exocyclic or endocyclic modes, we refer to them as *Exo* and *Endo* alkylations, respectively. Recently, in a general treatment of ring closures,[1,2] we suggested on stereoelectronic grounds that 5-*Endo*-Trigonal processes, (**6**), were disfavoured, whereas 6-*Endo*-Trigonal closures, (**7**), were favoured ring closures. Since the *Endo*-alkylation, (**3**) to (**5**), is stereoelectronically similar to the processes (**6**) and (**7**) it was possible to predict that the *Endo*-alkylation of a ketone to a 5-membered ring would be disfavoured, whereas the formation of a 6-membered cyclic ketone, by analogy with the 6-*Endo*-Trig process (**7**), in this way would be favoured. We now present evidence that this is true. Thus inverse Markownikov addition of hydrogen bromide to the ketone (**8**)[3] gave (90%) the ketobromide (**9**), b.p. 130 °C at 25 mmHg; ν (neat) 3000m and 1705s $cm^{-1}$; δ ($CDCl_3$) 1·2 (s, 6H), 2·2 (s, 3H), and 2·2 and 3·35 ($A_2B_2$ m, 4H total), which was converted into both potassium and lithium enolates (**10**, M = K or Li) with potassium

t-butoxide (1·5 equiv.) in t-butyl alcohol–ether and lithium di-isopropylamide (1·25 equiv.) in ether at 25 °C. In both cases the sole reaction product was the enol ether (**11**) (>70% isolated), ν (neat) 3000s, 1670s, 1220s, 1060s, and 820s $cm^{-1}$; δ ($CDCl_3$) 1·2 (s, 6H), 1·80 (t, *J* 7 Hz, 2H), 3·75 and 4·05 (ABq, *J* 2 Hz, 2H), and 4·0 (t, *J* 7 Hz, 2H), which was very sensitive to hydrolysis and therefore converted into the 2,4-dinitrophenylhydrazone of (**13**), m.p. 102—103·5 °C.† Spectroscopic analysis of the reaction mixture from (**10**) showed the absence (<3%) of the cyclopentanone (**12**).




In contrast to this result, conversion of the ketone (**14**)[4] into the bromide (**15**), b.p. 100 °C at 5 mmHg, ν (neat) 2950 m and 1705s $cm^{-1}$; δ ($CDCl_3$) 1·05 (s, 6H), 1·65 (m, 4H), 2·1 (s, 3H), and 3·35 (m, 2H), and thence into the enolates (**16**, M = K or Li) under the same conditions as before gave only the cyclohexanone (**17**),[5] (>95% by n.m.r.), converted into the known 2,4-dinitrophenylhydrazone, m.p. 136—138 °C.[6]

The remarkable difference between these two cyclizations results from stereoelectronic control of the alkylation of the ambident nucleophile, *i.e.* the enolate ion. For such an ion, (**19**), carbon alkylation requires approach of the electrophile perpendicular to the plane of the enolate, whereas oxygen alkylation requires approach in the plane of the enolate. Consequently, in the five-membered ring case approach of the alkylating centre to the carbon site in the reasonable *O*-metallated species, existing as *s-cis* and *s-trans* forms shown in planar form (**20**), is sterically difficult‡ compared to its approach in the plane to the oxygen site, (**20**) to (**22**), yielding the observed enol ether product. On




† All new crystalline compounds have given adequate combustion data.

‡ This difficulty has the same stereoelectronic origin as the disfavouredness of 5-*Endo*-Trig ring closures (ref. 1). These results indicate that the remaining direction for approach of an electrophile to the oxygen atom, *i.e.* perpendicular to the plane in (**19**), is in some way disfavoured relative to the in-plane approaches.

the other hand, in the six-membered precursor (**21**) the carbon alkylation is sterically possible, for the same reasons as those by which 6-*Endo-Trig* processes for ring closure are favoured,[1,2] namely that the extra bond length in (**21**) enables a near perpendicular approach to the enolate and hence carbon alkylation.[7]

The natural extension of these ideas to the four- and three-membered cases for *Endo*-alkylation predicts, following the Rules of Ring Closure,[1] is that processes described by (**23**) and (**24**) would be disfavoured. In the four-membered case, evidence has been presented that enol ether formation and participation of dipole (**25**) are the major processes.[8] The three-membered case, which is involved in the classical Faworskii rearrangement,[9] may similarly involve the favoured product enol ether (**27**) or the dipole (**28**).[10] In contrast to these limitations on *Endo*-alkylations, in accord with the Rules,[1] the *Exo*-alkylations, (**2**) to (**4**), are all favoured processes with many literature precedents for forming rings from 3 to 7 members.[11]

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