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INTRAMOLECULAR MICHAEL ADDITION OF CYCLIC β-KETOESTER ON CONJUGATED OLEFINIC KETONE, A STEREOELECTRONICALLY CONTROLLED PROCESS

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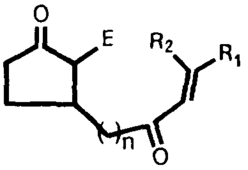
ABSTRACT. A study on the base-catalyzed intramolecular Michael addition of cyclic β-ketoester enones 9 and 10 (n = 0-3, $R_1 = R_2$ = H and/or CH_3) is reported.

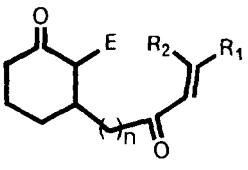
In the nucleophilic addition on conjugated olefinic ketones (enones), stereoelectronic effects predict that the intermediate enolate should first be generated in a conformation where the newly formed bond is parallel with the π system of the enolate[1]. Stereoelectronic parameters predict also that the anion of a six-membered β-ketoester should react with an electrophile to generate the alkylated product either in a chair (axial approach) or in a twist-boat (equatorial approach) form[2]. On that basis, the intramolecular Michael addition of the enolate of a cyclic β-ketoester on an enone can theoretically take place via four different transition states to produce the enolates 1-4 in the conformation shown in Scheme 1. Further protonation then yields the two cis and the two trans isomeric bicyclic products 5-6 and 7-8. The formation of these four isomeric products is due to the fact that the β-ketoester can react from its α or β-face and that the enone can approach the β-ketoester enolate in two different manners (exo or endo). When $R_1 = R_2$ = H only one cis (5 = 6) and one trans (7 = 8) isomers are possible, but then each isomer can be produced via two different transition states.

The above considerations based on stereoelectronic arguments indicate a high degree of conformational restriction at the transition state level and steric effects should be quite different for each mode of cyclization. A high degree of discrimination can therefore be anticipated. As a result, new synthetic strategies for the stereocontrolled construction of polycyclic molecules may be discovered from this kind of study. Also, the importance of stereoelectronic control in these processes can be tested. With this in mind, we have studied the cyclization of the five- and the six-membered β-ketoester-enones 9 and 10 (n = 0-3; R_1,R_2 = H or H and CH_3). We wish to report our preliminary findings.



9

(E=COOCH$_3$)



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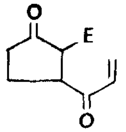
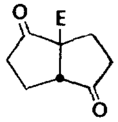
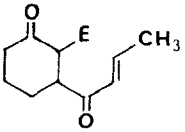
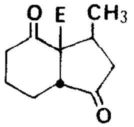
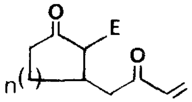
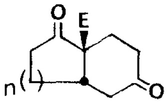
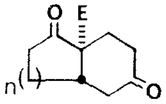
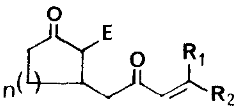
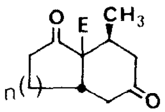
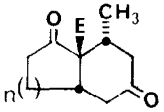
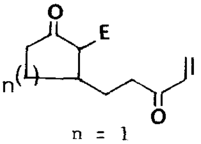
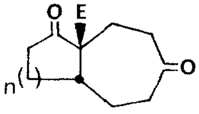
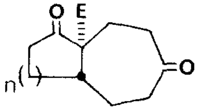
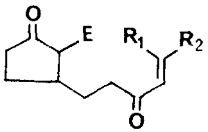
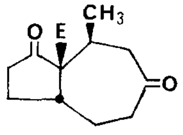
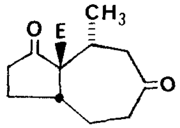
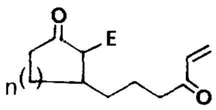
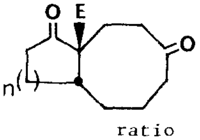
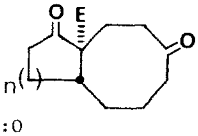
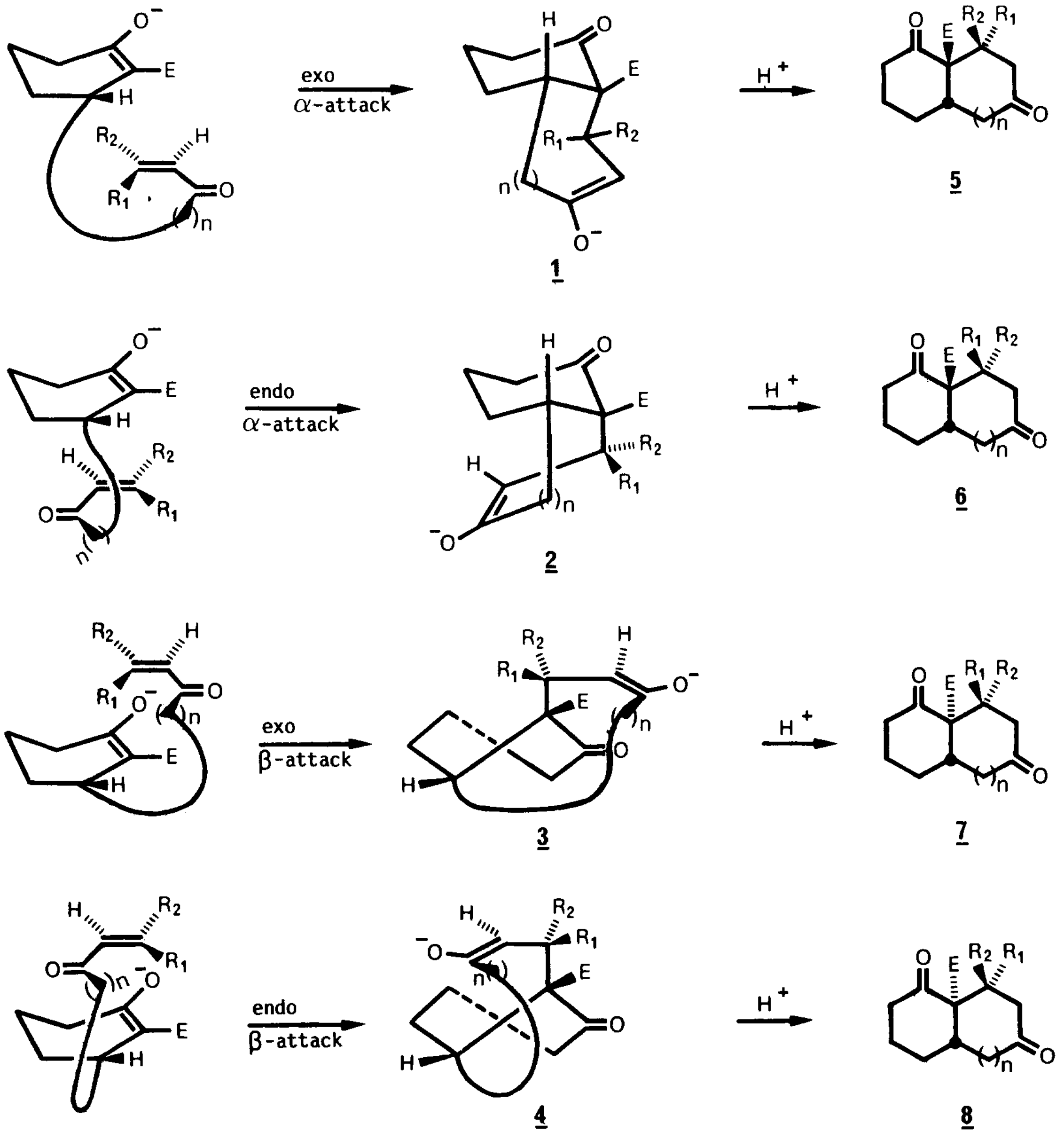
Our study on the cyclization of the various substrates are shown in Table 1. The results obtained are readily explained on the basis of the rational summarized in Scheme 1.

TABLE 1. CYCLIZATION OF β-KETOESTER-ENONES (E = $COOCH_3$)

Entry	Starting material	Method	Reaction time (h)	Yield	Products
1		A	0.5	0	
2		C	120	0	
					 
3	n = 1	A	1	70	ratio 1:0
4	n = 2	A	1	89	ratio 1:0
					 
5	n = 1, R_1 = H, R_2 = CH_3	B	1	71	ratio 1:2.5
6	n = 1, R_1 = CH_3, R_2 = H	B	24	27	ratio 1:1
7	n = 2, R_1 = H, R_2 = CH_3	C	2	95	ratio 1:4
8	" " "	A	2	97	ratio 1:2
9	n = 2, R_1 = CH_3, R_2 = H	A	144	27*	ratio 1:1.5
					 
10	n = 1	A	4	88	ratio 1:0
11	n = 2	C	5	40	ratio 2:1
12	n = 2	A	5	57	ratio 5:1
					 
13	R_1 = H, R_2 = CH_3	B	18	50	ratio 1:9
14	R_1 = CH_3, R_2 = H	B	96	2	ratio 1:9
					 
15	n = 1	A	48	14	ratio 1:0
16	n = 2	A	48	25	ratio 1:1

* : Large percentage of starting material recovered. A: 0.2 equiv. Cs_2CO_3, CH_3CN, r.t., 2 x 10^{-3} M. B: 2.0 equiv. Cs_2CO_3, CH_3CN, r.t., 2 x 10^{-3} M. C: 0.2 equiv. Cs_2CO_3, THF:DMF (1:1), r.t., 2 x 10^{-3} M.

Formation of a cyclopentanone ring by an intramolecular Michael reaction (entries 1 and 2) does not take place. This is in agreement with the fact that it does not seem possible to produce intermediates 1-4 in the conformation shown when $n = 0$.[3] Formation in high yield of *cis* six- membered ketones (entries 3 and 4) show that when $n = 1$, formation of intermediate 1 and/or 2 are possible, but not that of 3 and 4. This is in accord with what can be predicted on the basis of steric arguments. The results obtained in entries 5-9 demonstrate that the *endo* process is favored over the *exo* process when the starting β-ketoester ring is five- and six-membered. The large difference between the ease of cyclization (and yield) of *transoid*



(E=COOCH$_3$)

SCHEME 1

enone (entries 5, 7 and 8) with that of cisoid enone (entries 6 and 9) shows that when n = 1, it is much easier to form 1 and 2 with R_1 = H and R_2 = CH_3 than with R_1 = CH_3 and R_2 = H. In the last situation, the six-membered enolate ring of 1 and 2 is in a boat like conformation with the methyl group oriented in a sterically unfavored flag pole position.

The formation of a cycloheptanone ring is also interesting. The cis bicyclic product is formed exclusively when the starting β-ketoester is five-membered (entry 10). When it is a six-membered ring (entries 11 and 12), the cis bicyclic product is again preferentially observed but the trans isomer can also be isolated. This is in accord with the fact that a β attack (exo and/or endo) yielding the trans isomer ought to be easier when the starting material has a ring which allows more conformational mobility. This should be the case for a cyclohexane ring by comparison with a cyclopentane ring. Results described in entries 13 and 14 show that the cyclization of transoid enone takes place readily, but not that of the cisoid enone and the reasons must be similar to those previously discussed for entries 5-9. The result observed in entry 16 shows that the trans and the cis isomers are formed with equal ease when the newly formed ring is eight-membered. Again this indicates that a β attack (endo and/or exo) is allowed when the chain length is long enough (cf. 3 and 4, n = 3). Finally, the specific formation, although in low yield of a cis bicyclic octanone (entry 15) indicates that a five-membered ring β-ketoester lead to a higher degree of stereochemical control than the six-membered ring analog (entry 16).[4-6,8]

Acknowledgements

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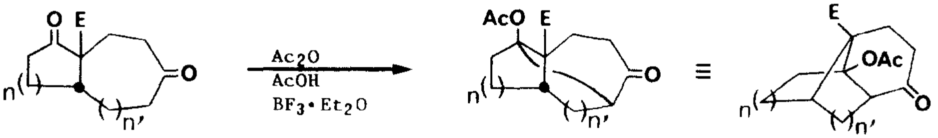
References and Notes

1. For a general reference see: P. Deslongchamps. Stereoelectronic Effects in Organic Chemistry". Organic Chemistry Series, Vol. 1. Edited by J.E. Baldwin, Pergamon Press, Oxford, England, 1983. pp. 221-242.
2. See reference 1, pp. 274-284.
3. For a theoretical study, see, G.W.L. Ellis, D.F. Tavares, and A. Rauk. Can. J. Chem. 63, 3510 (1985).
4. All spectra (250 MHz, ^{1}H and ^{13}C, 80 MHz ^{1}H nmr, ir and high resolution mass spectra) are in agreement with the assigned structures.
5. Authentic samples for the cis bicyclic compounds in entries 3-9 were obtained via a Diels-Alder reaction with 2-carbomethoxy-cyclohexenone and -cyclopentenone [cf. H.J. Liu and T.K. Ngooi. Can. J. Chem. 62, 2676 (1984)].
6. The cis junction of the bicyclic compounds in entries 10-15 was demonstrated by carrying the following intramolecular aldol condensation.[7]



7. A. Bélanger, Y. Lambert, and P. Deslongchamps. Can. J. Chem. 47, 795 (1969).
8. In entries 13-14, the relative configuration of the secondary methyl group of the major and minor isomers has not been rigorously established respectively.

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