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REGIOSPECIFIC MICHAEL ADDITIONS TO α-METHYLENE CYCLOPENTENONES

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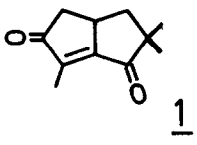
Abstract: Nucleophiles add in a Michael fashion to α-methylene cyclopentenones regiospecifically at the exocyclic cisoid-enone double bond.

Danishefsky[1] has demonstrated that the direction of Michael additions to unsymmetrical enedione 1 is governed by strain in the developing enolate, the formation of enolate 2 with an SP^2 bridgehead carbon being inhibited compared to the less strained enolate 3. Thus products from such reactions are uniformly derived from 3. It is extremely interesting to consider the difference in regiochemistry in the addition reaction as depicted in 4. Nucleophilic attack at the bridgehead carbon X to give 3 is, in fact, an addition to the endocyclic transoid-enone double bond, while the same process at Y yielding 2 is attack at the exocyclic cisoid-enone double bond.



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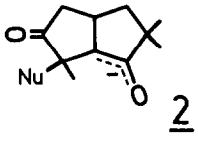

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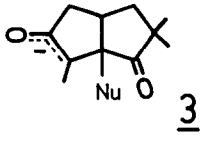

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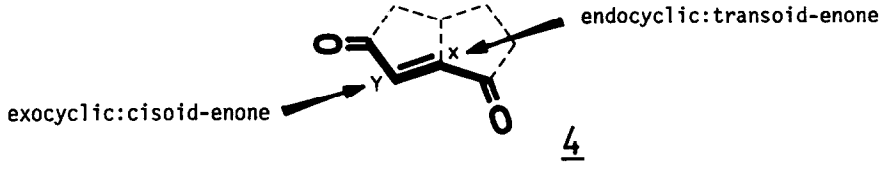

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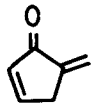
Michael additions to both types of enones are well documented, specific examples being the *in vitro* Michael additions of L-cysteine to naturally occurring α-methylene-γ-butyrolactones (exocyclic:cisoid)[2] and cyclopentenones (endocyclic:transoid),[3] which explain the biological activities of these

compounds. However, apart from Danishefsky's investigation, a report on the direct competition of these two Michael pathways is not precedented. In order to assess this, a suitable Michael acceptor molecule bearing both endocyclic and exocyclic enones must be employed, and unlike the bicyclic enedione 1, the system should give rise to enolate intermediates with comparable strain. In this Letter we would like to present the results of such a study.

Since developing the convenient 3-carbon annelation method for the synthesis of α-methylene cyclopentenones (eg. 5)[4] we have perceived this type of dienone to be a suitable model for the study of the regiospecificity of Michael additions. Hence compound 6 was selected for its stability[5] and the following steric reasons. Inspection of molecular models of molecule 6 indicated almost no strain in either of the transition states leading to the enolate 7 or 8, which are expected from nucleophilic attack at the two trigonal centres (see arrows in 6). Nevertheless, nucleophilic addition to the endocyclic double bond of the acceptor molecule 6 should lead to an electronically more stable enolate 7, yet, as will be seen later, the products of the reactions were not controlled by this predicted effect at all.



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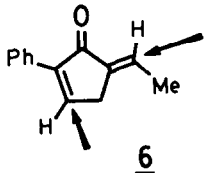

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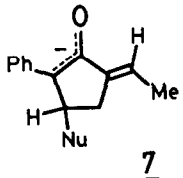

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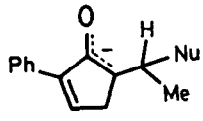
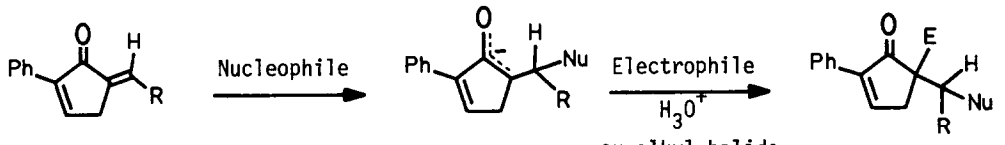


8

α-Methylene cyclopentenone 6 was prepared in very good yield by our previously described method.[6] The Michael addition reactions proceeded smoothly in THF solution at -78° when a solution of 6 was added to a solution of two molar equivalents of nucleophile.[7] It was very interesting to find that the NMR spectra of the crude Michael adducts showed complete absence of the easily distinguishable exocyclic vinyl proton, originally a quartet at δ 6.76 in 6. Purification of these crude materials gave products identified as 9,[8] which proves that the Michael addition specifically occurred at the exocyclic double bond of the cisoid-enone. As the TABLE indicates, apart from protonation we were able to trap the intermediate enolate 8 with other electrophiles. This is demonstrated in entries i and ii where products 9 (E ≠ H) were obtained.

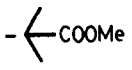
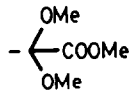
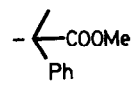
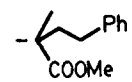
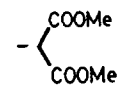
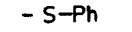
We also looked at the simpler (but not as good) model molecule 10. Again, additions cleanly produced only 12, showing that nucleophiles reacted preferentially at the exocyclic site.



6, R = Me
10, R = H

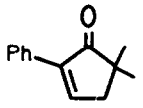
8, R = Me
11, R = H

9, R = Me
12, R = H

	Nucleophile	Electrophile	% of 9[a]	% of 12[a]
i.		a. H_3O^+	91	90
		b. CH_3I	85	76
		c. $H_2C{=}CH{-}CH_2{-}Br$	82	74
		d. $Ph{-}CH_2{-}Br$	64	73
ii.		a. H_3O^+	90	71
		b. CH_3I	85	*b*
		c. $H_2C{=}CH{-}CH_2{-}Br$	81	*b*
		d. $Ph{-}CH_2{-}Br$	58	*b*
iii.		a. H_3O^+	84	73
		b. CH_3I	*b*	68
		c. $H_2C{=}CH{-}CH_2{-}Br$	*b*	77
		d. $Ph{-}CH_2{-}Br$	*b*	78
iv.		H_3O^+	86	72
v.		H_3O^+	82[c]	94[c]
vi.		H_3O^+	95[c]	97[c]

[a] The yields shown are isolated yields after purification by Prep. TLC (Silica gel, 7:3 CH_2Cl_2: hexane). Where several diastereomers were possible it was found that one isomer always predominated (indicated by NMR). Separation of isomers were performed in cases 12-iii-b, 12-iii-c, and 12-iii-d, each of which afforded two stereomers, but no attempt was made to assign their stereochemistry. [b] This reaction has not been performed. [c] The reaction can be conducted either in THF (LDA as base) at -78° or in MeOH (NaOMe as base) at room temperature, the yield shown being from the latter reaction condition.

The regiospecificity of the reaction was confirmed when cyclopentenone 13[9] was subjected to the same reaction conditions as described above. Without the competition of the exocyclic double bond, nucleophiles (i, ii, v, and vi) were found to add to the enone 13 to give, after protonation, the pentanone 14 almost quantitatively.



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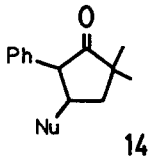

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In conclusion, while the site of Michael addition in the bicyclic enedione 1 is governed by steric factors in the resulting enolates, the same reaction with monocyclic dienones 6 and 10 occur specifically at the exocyclic double bond despite the fact that an electronically more favourable enolate could be formed from endocyclic attack. These results suggest that the same type of specificity is viable in the biological system.

Acknowledgement: We thank the National Research Council of Thailand for support of this work.

References

1. S.Danishefsky, M.Kahn, Tetrahedron Lett., 1981, 22, 485.
2. S.M.Kupchan, D.C.Fessler, M.A.Eakin, T.J.Giacobbe, Science, 1970, 168, 376.
3. I.H.Hall, K.H.Lee, E.C.Mar, C.O.Starnes, J.Med.Chem., 1977, 20, 333.
4. T.Siwapinyoyos, Y.Thebtaranonth, J.Org.Chem., 1982, 47, 598.
5. Aryl substituted α-methylene cyclopentenones are quite stable while others are not.
6. Compound 6 and its geometrical isomer were prepared according to the method described in ref. 4 with nearly quantitative yields in each step.
7. Lower yields of 9 were observed when equimolar amounts of reactants were employed. This is probably due to competition between the nucleophile and the emerging enolate 8 for the acceptor 6. Hence a high nucleophile concentration was required.
8. All compounds described in this Letter display quite satisfactory physical data.
9. P.Prempree, T.Siwapinyoyos, C.Thebtaranonth, Y.Thebtaranonth, Tetrahedron Lett., 1980, 21, 1169.

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