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CONTROLLED FUNCTIONALIZATION OF CYCLOHEPTA-1,3-DIENE: CONFORMATIONAL ANALYSIS OF CYCLOHEPTENONES AND DERIVED CYCLOHEPTADIENOLATE ANIONS

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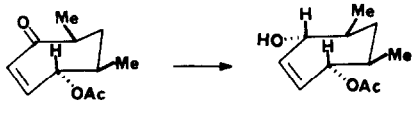
Abstract: Analysis of the conformations of some cycloheptenones and cycloheptadienolates, and the relationship between conformation and stereochemistry during certain reactions, is discussed.

The cycloheptane ring presents some interesting possibilities in organic synthesis, but has the reputation of being very awkward in terms of stereocontrolled functionalization, largely owing to the difficulties associated with its conformational analysis.[1] Introduction of unsaturation, as in cycloheptene or cycloheptenone, leads to some degree of conformational rigidity, and it may be anticipated that useful methodology can be developed provided the conformational factors which are at work during certain functional group manipulations are understood.

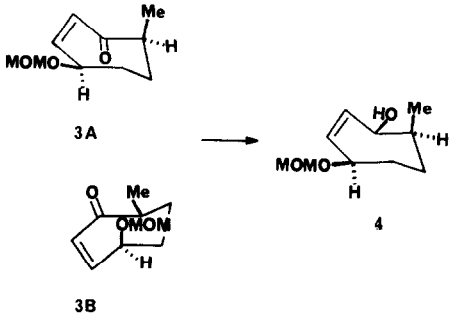
In the preceding communication[2] we described the outcome of certain reactions of cycloheptenone derivatives, which showed good stereocontrol, and which led to the preparation of intermediates which are appropriate for synthetic approaches to the (±)-Prelog-Djerassi lactonic acid and, therefore, a number of important macrolide antibiotics.



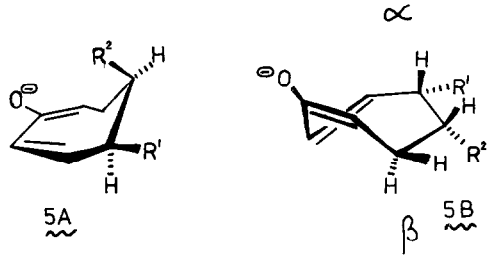
1 2

First, we shall consider the sodium borohydride reduction of the cycloheptenone derivatives (**1**) and (**3**) to give alcohols (**2**) and (**4**), respectively. Molecule (**1**) can unambiguously adopt a chair conformation in which all substituents are equatorial. Consequently, stereoelectronically controlled attack of the hydride reducing agent along the axial vector[3] leads to the equatorial alcohol shown in (**2**). With compound (**3**) the situation is rather different, since two conformations, (**3A**) and (**3B**) are possible, each having one axial and one equatorial substituent. However, the ^{1}H NMR spectrum of (**3**) clearly shows H(4) to be axial, with $J_{4,5}$ = 9.9 Hz. Thus, the preferred conformation is (**3A**), with OR group equatorial

and CH_3 axial. Borohydride reduction of (**3A**) occurs cleanly, again by stereoelectronically controlled axial attack to give (**4**) (see preceding communication), exactly analogous to the reduction of (**1**). These results provide convincing evidence that (**3**) has the relative stereochemistry shown, and we are now in a position to analyze the methylation of substituted cycloheptenone derivatives.

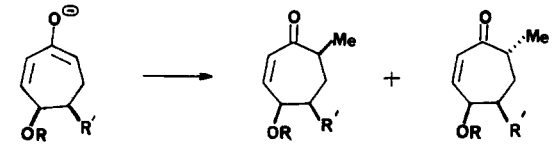


The enolate derived from cycloheptenone is essentially a cyclohepta-1,3-diene derivative, and its reactivity may be analyzed on the basis of the diene conformations. Spectroscopic evidence has been cited as indicative of planar[4] or twisted[5] diene conformations, (**5A**) or (**5B**), and (drawn as enolate for convenience), is therefore not useful as a guide to reactivity. Cyclofunctionalization results obtained in our own laboratory[6] are strongly suggestive of a twisted diene conformation at relatively low temperatures, and the present enolate alkylation results are best interpreted in terms of that conformation. This is also consistent with simple molecular models which indicate appreciable angle strain in the planar fully conjugated diene, which is relieved on allowing twisting, and which in turn is accompanied by partial deconjugation (interplanar angle is ca 45^{o}). Thus, assuming the dienolates (**6**) and (**7**) adopt the twisted conformation (**5B**) we can explain the stereochemistry of methylation.



As can be seen by inspection of (**5B**), the α-face of the twisted diene is concave. Approach of the electrophile (CH_3I) is clearly preferred at the convex β-face. With enolate (**6**) the methoxymethyl ether substituent has quasi equatorial orientation (R^1 in **5B**) so that methylation on the β-face will lead to (**8a**), which indeed is the observed major product[1] (3.5:1 ratio). Introduction of a methyl substituent at C(5), as in enolate (**7**) does not significantly

alter this argument, since it is quite remote from the reaction site. In fact, the ratio (**8b**):(**9b**) (ca 10:1) is rather better in this case, again favoring attack on the convex β-face. The improved stereoselectivity might well result from an enhanced equilibrium population of the twisted conformation, since the planar conformation for (**7**), assuming a preference for equatorial benzoyloxy group, now shows a quite pronounced transannular non-bonded interaction between the ring (diene) carbons and the 5-methyl group, as can be judged by inspection of the structure shown for (**5A**).



6 R = MOM
R' = H

7 R = COPh
R' = Me

8
(a) R = MOM ,
(b) R = COPh ,

9
R' = H
R' = CH_3

In conclusion, there appears to be a definite preference for (a) axial attack during borohydride reduction of substituted cycloheptenones, and (b) a twisted conformation for cycloheptadienolate which is preferentially alkylated from the convex face. The preference for axial attack on the enone carbonyl in this series parallels the reactivity of cyclohexanone derivatives, but contrasts with the larger ring sizes (⩾ 8-membered) where there is observed a preference for peripheral attack.[7]

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References and Notes.

1) E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, Conformational Analysis, American Chemical Society, Washington, DC, 1981, pp 207-210, and references cited therein.

2) A. J. Pearson and H. S. Bansal, preceding paper in this issue.

3) In the cycloheptenone series, the shape of the molecule is such that equatorial addition to the carbonyl would probably be more favored on steric grounds alone, since the torsional interaction between nucleophile and protons at C(2) and C(7) is probably less destabilizing than the interaction being a nucleophile on the axial trajectory and the axial protons at C(4) and C(6). Various reasons have been suggested for the preferred axial addition of nucleophiles to cyclohexanone derivatives, and the picture is not clear. See, for example: M. Cherest and H. Felkin, Tetrahedron Lett., 1968, 2205; A. S. Cieplak, J. Am. Chem. Soc., 1981, 103, 4540; P. Deslongchamps, Steroelectronic Effects in Organic Chemistry, Pergamon Press, 1983, Chapter 6.

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