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ORGANOCUPRATE REACTIONS OF ENONE LACTONES.
II. REGIOCHEMICAL EFFECT ON REDUCTIVE CLEAVAGE.

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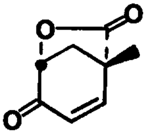
Abstract: The course of organocuprate conjugate addition and reduction in cyclohexenones made conformationally rigid by attachment of a 1,3-lactone is shown to depend on the regiochemistry of such enones.

In the preceding paper we described the conjugate addition of organocuprates to enone lactone 1. Such additions were accompanied by some reductive cleavage, and we were interested in determining whether the differing regiochemistry of enone 2 would influence the extent of reduction. We now report that 2 undergoes such reduction almost exclusively.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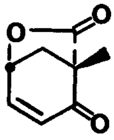
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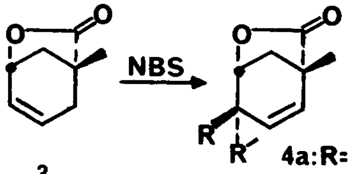

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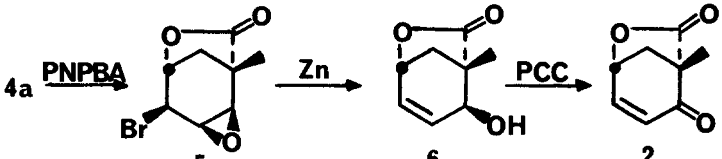
4a: R=Br, R'=H
4b: R=H, R'=Br

Enone lactone 2 was prepared from intermediates described in the preceding paper.[1,2] Thus treatment of unsaturated lactone 3 with 1.0eq of N-bromosuccinimide in carbon tetrachloride containing benzoyl peroxide (1.0hr at reflux over a 250-watt sunlamp) gave bromolactones 4a (80% yield; mp 62-63.5°, ether-pentane) and 4b (8% yield; mp 81°, ether-pentane), after chromatography on silica gel. Remarkably, no formation of the regioisomeric bromides was observed.[3]



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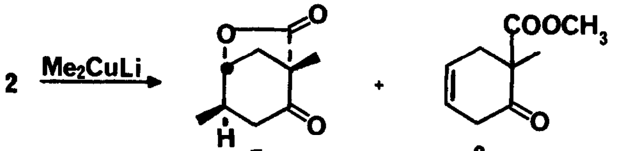
Lactone 4a was epoxidized by exposure for 15hr to 2eq of p-nitroperbenzoic acid in refluxing dichloroethane containing a trace of TBP[4], to give epoxide 5 (61% yield; mp 146-148°, ether-ethyl acetate) after trituration of the crude product with cold ether. Treatment of 5 with zinc dust in acetic acid gave allylic alcohol 6 (80% yield; mp 55-57°, ether-pentane) after trituration with cold isopropyl ether.[5] Alcohol 6 was converted to enone lactone 2 (83% yield; mp 77-79°, sublimed at 0.10mm and 80-90°) by oxidation with sodium acetate-buffered pyridinium chlorochromate.



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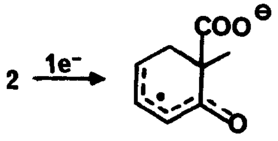
Exposure of enone 2 to 2eq of lithium dimethylcuprate in ether at 0°, followed by workup with aqueous ammonium chloride, gave ketolactone 7 (9% yield; mp 72-74°, ether-pentane), and acidification, extraction and treatment with ethereal diazomethane additionally furnished keto-ester 8 in 60% yield after chromatography on silica gel.

While conjugate addition occurs in this instance, reduction is clearly the preferred reaction pathway, in contrast with the case of enone 1. It is possible that the reduction of enone 2 is more favored because cleavage after electron transfer (2→9) would lead to a more highly delocalized species than would be obtained from the regioisomer (1→10), thus lowering the activation energy for such a process.



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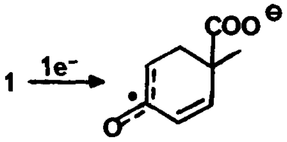

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In summary, our results suggest that organocuprate conjugate addition may be feasible for cyclohexenones substituted at the 6-position with otherwise reducible groups, and is less likely to succeed in analogous 4-substituted compounds.[6] It would clearly be desirable to have additional examples suitable for direct comparison.

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References and Notes

1. New compounds had spectral data consistent with assigned structures, and crystalline compounds gave satisfactory elemental analyses. Capillary melting points were determined on a Büchi "schmelzpunktbestimmungsapparat" and are uncorrected.
2. For a possible alternative synthesis, see: G.W. Holbert and B. Ganem, J. Org. Chem., 41, 1655 (1976).
3. Chemical shifts of vinyl protons (ppm downfield from TMS): 4a, 5.85(m); 4b, 5.81(m).
4. 4,4'-thiobis(6-t-butyl-3-methylphenol)--Y. Kishi, M. Aratani, H. Tanino, T. Fukuyama, T. Goto, S. Inoue, S. Sugiura, and H. Kakoi, J. Chem. Soc., Chem. Commun., 1972, 64.
5. Chemical shifts of vinyl protons: 5.90(dd, J=1,1.5Hz), 6.42(dd, J=1.5,2Hz). No reduction of the lactone was observed.
6. For the organocuprate reduction of 4-acetoxy-3-methylcyclohexenone, see: R.A. Ruden and W.E. Litterer, Tetrahedron Lett., 1975, 2043.

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