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# MICHAEL ADDITION REACTIONS OF ANGELICA LACTONE

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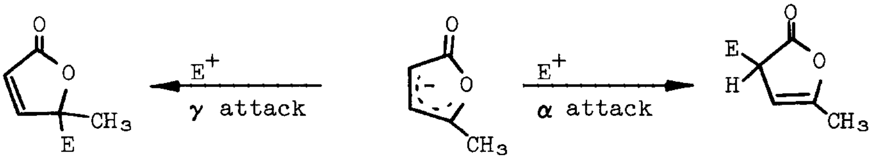
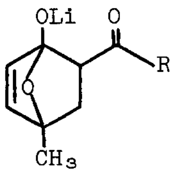
As a result of their vast physiological potential[1], butenolides have received much attention.[2] We are currently examining the reactions of butenolide anions. Butenolide anions such as 1 might react with electrophilic reagents at either the α or γ position.



1

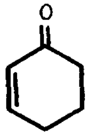
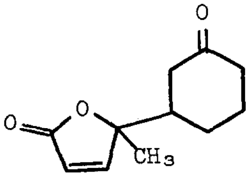
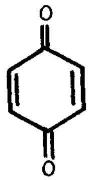
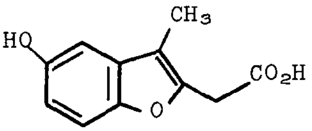
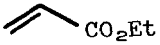
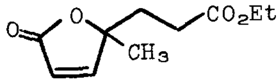
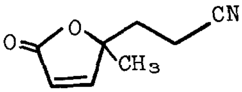
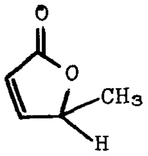
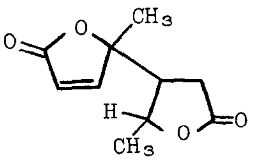
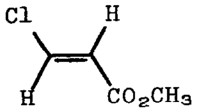
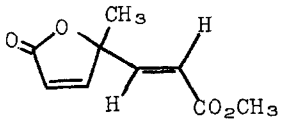
The reaction of 1 with alkyl halides,[3] aldehydes[4] and ynamines[5] occurs exclusively at the α position. We wish to report that the Michael addition of butenolide anions with a wide variety of Michael acceptors occurs <u>exclusively</u> at the γ position,[6] as shown in the Table below.

One possible explanation for the course of this intriguing reaction is that an initial, reversible α addition occurs, followed by γ addition. Another possibility might be the formation of a bicyclic intermediate 2 which could break down to form the observed product.



2

Table

| Reactant | Conditions[8] | Product | Yield[9] |
|---|---|---|---|
|  | THF/-78°C<br>LDA |  | 75% |
|  | THF/-78°C<br>LDA |  | 70% |
|  | THF/-78°C<br>LDA/ZnI$_2$ |  | 60% |
|  | THF/-78°C<br>LDA/ZnI$_2$ |  | 60% |
|  | THF/-78°C<br>LDA |  | 50%[10] |
|  | THF/-78°C<br>LDA |  | 85% |

A third possibility[7] might be that the enolate reacts as an alkoxy furan, wherein substitution α to the ring oxygen might have been anticipated. In this case, however, γ alkylation should also be observed. Reaction of 1 with methyl iodide under conditions identical to those used for Michael additions gives a mixture of α,α dialkylated lactone, α-alkylated lactone and starting material. Evidence for the hypothesis involving bicyclic intermediate 2 can be found in the work of Nazarov[11] where a bicyclic product from a Michael addition was actually isolated. In our case, the utilization of low temperature trapping experiments with acetic anhydride failed to produce any acetylated bicyclic product. In a typical experiment, a 1 M solution of angelica lactone was added to lithium diisopropyl amide (1 M in THF) at -78°C at a rate of 1 mmole/min. The solution was stirred five minutes and ethyl acrylate was then added in THF at -78°C. The solution was allowed to warm to 0°C, quenched with acetic acid and partitioned between ether and water. The organic layer was dried over sodium sulfate, filtered and concentrated. The crude product was chromatographed on silica gel using ether. The identity of this product (NMR: δ ($CDCl_3$) 1.25 (t, 3H), 1.5 (s, 3H), 2.2 (m, 2H), 4.1 (q, 2H), 6.05 (d, 1H), 7.45 (d, 1H). IR (film) 1740, (1760 $cm^{-1}$) was confirmed by hydrogenation of the butenolide[12] and independent synthesis of the resulting γ-lactone by reaction of γ-keto pimelic ester[13] with methyl magnesium bromide, followed by lactonization. Experiments to determine the generality of Michael addition reactions with substituted butenolides and to apply this reaction to natural products synthesis are in progress.

## ACKNOWLEDGEMENT

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## REFERENCES AND NOTES

1. Among the many compounds which contain the butenolide moiety are elephantopin: S. M. Kupchan, et al., J. Am. Chem. Soc., **88**, 3674 (1966) which is a tumor inhibitor and liatrin: S. M. Kupchan, et al., J. Org. Chem., **38**, 1853 (1973) which exhibits antileukemic properties.

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6. Examination of the olefinic region of the NMR spectrum of crude reaction product showed no evidence of other products.
7. We thank a referee for suggesting this possibility.
8. One equivalent of $ZnI_2$ was needed to supress formation of side products.
9. This refers to compounds purified by silica gel column chromatography.
10. A low yield (10%) dimerization of angelica lactone has been reported by A. Hornfeldt, *Arkiv. Fur Kemi*, **28**, 571 (1967). The NMR spectrum reported is identical to ours.
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