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ENOL CARBONATES. WEAKLY NUCLEOPHILIC PRECURSORS OF SITE-SPECIFIC ENOLATES

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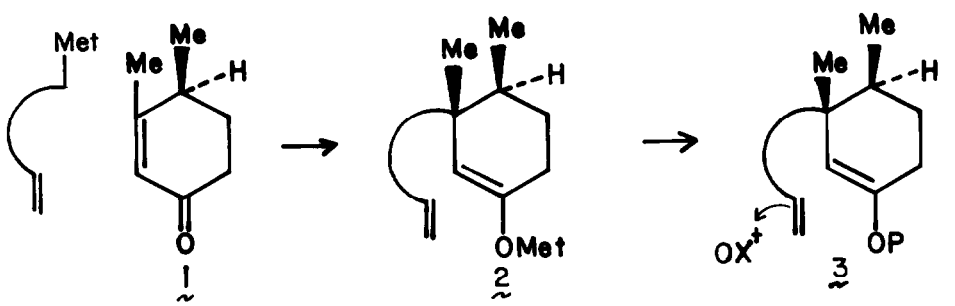
Abstract Examples of trapping of site-specific enolates by enol methoxycarbonylation are described. Selective operations at a remote double bond in the presence of the enol carbonate functionality have been realized. Site-specific enolates can be retrieved from the enol carbonates.

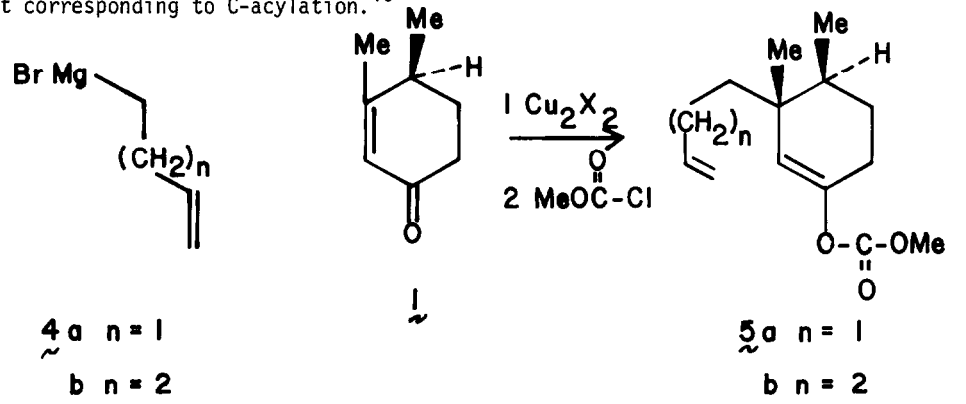
The first systematic study on the generation, maintenance and exploitation of site-specific enolates was described by Stork and associates through the reductive alkylation of enones.[1,2] Important advances in the generation of site-specific enolates by conjugate addition were provided by Boeckman[3] and Coates[4]

In addition to the direct "trapping" of such kinetically generated enolates, there have been developed a variety of enolate equivalents (silyl enol ethers,[5,6,7] vinyloxyboranes,[8] and enol acetates[9]). These systems allow for storage of a site-specific enolate as a neutral compound in a form which lends itself to purification. Needless to say, for such systems to be useful, there is to be allowed no serious erosion of positional specificity in the retrieval of the enolate" from the "enolate equivalent".

The investigation described herein was occasioned by our interest in a total synthesis of the novel indolic terpenoid, aflavanine.[10] The target system 3 was to be generated by conjugate addition of an unsaturated organometallic reagent to the enone 1 followed by "trapping" of the metalloenolate 2. *To this now familiar scenario was added the important proviso of the feasibility of achieving electrophilic reaction on the isolated rather than the "enolate" like double bond of intermediate 3.* In the light of its well known nucleophilicity,[11,12] the conventional silyl enolate equivalent appeared to be ill suited to our needs. A solution to this problem is described below.



Grignard reagents 4a and 4b were generated in ether in conventional ways, from the corresponding, commercially available, bromoolefins The ethereal solution of Grignard reagent was added to a solution of the enone in 1 1 dimethyl sulfide-diethyl ether, containing 10 mole % of cuprous iodide. The resultant metalloenolate 2 was quenched with methyl chloroformate (0°→rt) to afford 90% yields of the enol carbonates 5a and b [14,15] Under these conditions, we could detect no product corresponding to C-acylation.[16]



4a n = 1
b n = 2

1

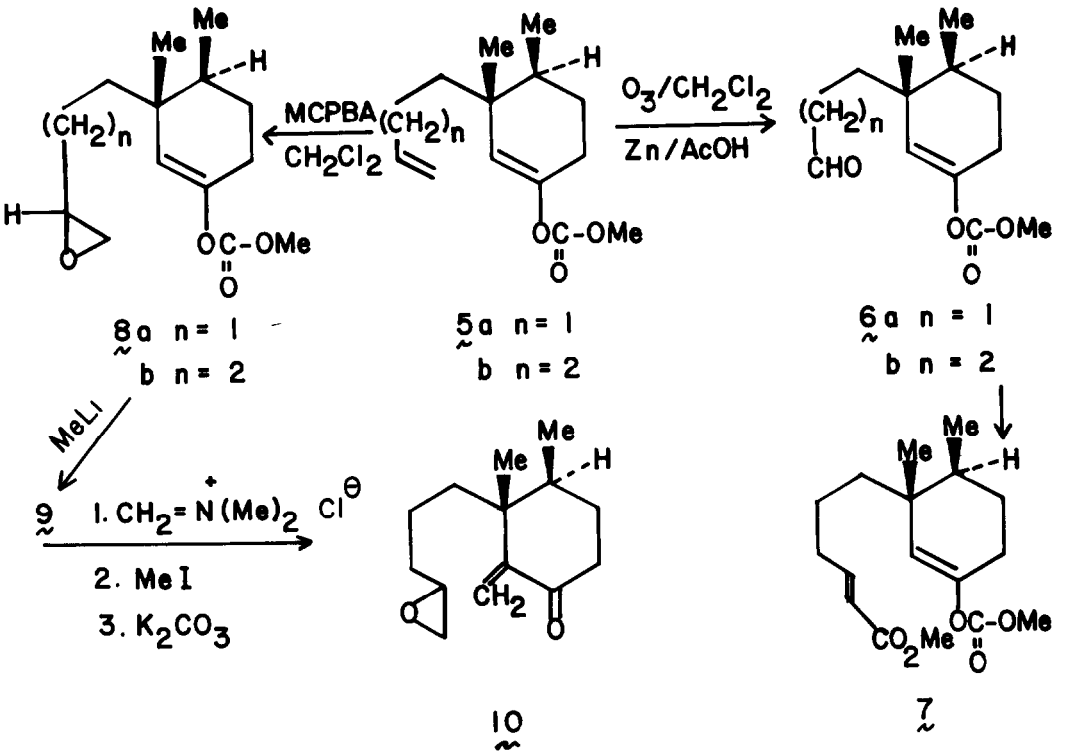
5a n = 1
b n = 2

Selective ozonolysis of 5a or 5b afforded, very cleanly, the aldehydo enol carbonates, 6a and b [14] The synthetically relevant aldehydo enol carbonate 6b, was subjected to Emmons condensation to afford 7 (93%) yield. This reaction testified favorably to the stability of the enol carbonate linkage. Similarly, reaction of 5a or b with m-chloroperoxybenzoic acid resulted in clean expoxidation of the "isolated" double bond with the formation of 8 Curiously, spectroscopic analysis seems to suggest the formation of only one epoxide of unknown relative stereochemistry.[14]

Retrieval of the site-specific enolate was demonstrated in a case which would appear to be particularly challenging Thus reaction of epoxy enol carbonate 8b with 3.5 eq of methyllithium at 0° in THF furnished a new metalloenolate, 9. Trapping of 9 with dimethyl (methylene) ammonium chloride,[17] followed by quaternization with metnyl iodide and elimination with aqueous potassium carbonate gave 10 in 47% yield from 8b

In summary, the enol carbonate method of storage of a site-specific enolate would seem to have significant promise in allowing for a reasonable range of reactions at distal olefinic centers. We have not investigated the relative rates of reaction in other systems Hence, we cannot comment on the extent to which the successes enjoyed herein are peculiar to the substrate However, since a range of acylating agents might, in principle, be employed, it would appear

that nucleophilicity of many enolate equivalents can be managed without undermining the site-specific retrievability of their corresponding enolates



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14. The structure of these compounds are consistent with their infrared, nmr and mass spectra, representative spectral data are given for:

5b δ ($CDCl_3$) 0.87, s, 3 H, 0 87, d, 3 H, J = 6 Hz, 3.78, s, 3 H, 4 95, m, 2 H, 5 18, s, 1 H, 5.75, m, 1 H, ppm, $\bar{\nu}$ (neat) 1765, 1695, 1640 cm^{-1}

6b δ ($CDCl_3$) 0.88, s, 3 H, 0 87, d, 3 H, J = 6 Hz, 3.80, s, 3 H, 5 23, s, 1 H, 9.80, t, 1 H, J $\tilde{=}$ 0.5 Hz, ppm, $\bar{\nu}$ (CCl_4) 1755, 1720, 1690 cm^{-1}

7 δ ($CDCl_3$) 0.85, s, 3 H, 0 87, d, 3 H, J = 6 Hz, 3 72, s, 3 H, 3 80, s, 3 H, 5.20, s, 1 H, 5.80, bd, 1 H, J = 15 Hz, 6 98 dt, 1 H, J_1 = 15 Hz, J_2 = 6 Hz , ppm, $\bar{\nu}$ (CCl_4) 1760, 1730, 1660 cm^{-1}

8 δ ($CDCl_3$) 0 85, s, 3 H, 0 84, d, 3 H, J = 6 Hz, 2 2, m, 2 H, 2 52, dd, 1 H, J_1 = 4 Hz, J_2 = 6 Hz, 2 81, dd, 1 H, J_1 = 2 5 Hz, J_2 = 6 Hz, 2.93, m, 1 H, 3 78, s, 3 H, 5 22, s, 1 H, ppm, $\bar{\nu}$ (CCl_4) 1760, 1680 cm^{-1}

10 δ ($CDCl_3$) 0 98, d, 3 H, J = 6 Hz, 1 03, s, 3 H, 2 71, dd, 1 H, J_1 = 4 Hz, J_2 = 6 Hz, 2.84, m, 1 H, 5 12, s, 1 H, 5.80, s, 1 H, ppm, $\bar{\nu}$ (CCl_4) 1680, 1600 cm^{-1}

15. We would like to thank B Bauer, of Yale University for providing this procedure

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