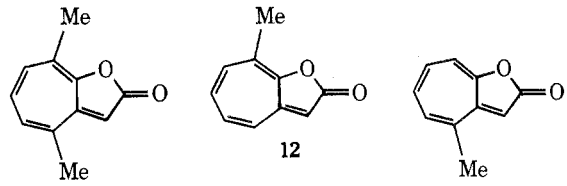

in a 3:1 ratio and were separated by column chromatography. The major isomer [mp 116–117 °C; NMR ($CDCl_3$) δ 7.40–6.70 (m, 4 H), 5.70 (s, 1 H), 2.43 (s, 3 H); ir ($CHCl_3$) 1740, 1600, 1500, 1265 cm^{-1}][9] was assigned structure **12** because hydrolysis to the acid and decarboxylation of the acid, using a modification of Seto's method,[5] gave 2,7-dimethyltropone[13] [NMR ($CDCl_3$) δ 7.40–6.65 (m, 4 H), 2.30 (s, 6 H); ir ($CHCl_3$) 2980, 1620, 1570, 1365, 1150 cm^{-1}]. The minor isomer **13** [mp 116–116.5 °C (lit.[14] mp 116.5–117.5 °C); NMR ($CDCl_3$) δ 7.21–6.67 (m, 4 H), 5.68 (s, 1 H), 2.39 (s, 3 H); ir ($CHCl_3$) 1750, 1595, 1495, 1260 cm^{-1}][9] gave 2,3-dimethyltropone [mp 59–60 °C (lit.[14] mp 58–59 °C); NMR ($CDCl_3$) δ 7.08–6.67 (m, 4 H), 2.31 (s, 3 H), 2.21 (s, 3 H); ir ($CHCl_3$) 2980, 1630, 1560, 1470, 1365, 1110 cm^{-1}] when submitted to the hydrolysis-decarboxylation procedure. The NMR spectral data of **12** and **13** establish that the signals from **9** and **10** which are shifted slightly downfield from those for the other seven-membered-ring protons result from the H_4 protons.

The comparable yields of **9** and **10** indicate that the fused ring of **8** does not significantly affect the direction of the initial Claisen rearrangement and that both pathways are equally facile. However, the 3:1 ratio of **12** to **13** observed in the FVP of **14** most likely results from a steric effect of the *o*-methyl group.

The production of **10** is especially significant since it possesses the ring system of several guaianolides and pseudoguaianolides, two important classes of sesquiterpene hydroazulenic lactones.[15]

It is not clear why the pyrolysis of aryl propiolates gives different products from those obtained from the pyrolysis of aryl propargyl ethers.[1] It should be noted, however, that the pyrolysis temperatures for the esters are ~200 °C higher than those for the ethers and this temperature difference could be an important factor in accounting for the different reaction pathways.

Acknowledgments. We thank the Mobil Foundation for partial support of this work.

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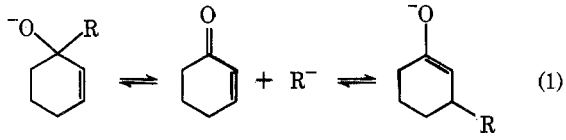
Walter S. Trahanovsky*
Susan L. Emeis, Andrew S. Lee
Department of Chemistry
Iowa State University of Science and Technology
Ames, Iowa 50011
Received September 14, 1976

Conjugate and Direct Addition of Ester Enolates to Cyclohexenone. Selective Control of Reaction Composition

Summary: Direct addition of ester enolates to 2-cyclohexen-1-one at −78 °C is reversible at higher temperatures to give products of conjugate addition.

Sir: Reactions of stabilized carbanions with α,β-unsaturated carbonyl systems have received considerable attention during the past decade. Both 1,2 and 1,4 additions have been realized with conjugated enones. For example, dithianes undergo exclusive 1,2 addition;[1] anions of protected cyanohydrins give mixtures of 1,2- and 1,4-addition products.[2] Thioacetal monosulfoxides derived from formaldehyde undergo 1,2 addition; however, higher homologues give predominately 1,4 addition.[3] Although these reactions have been developed into important synthetic methodology, experiments which clearly identify the requirements of direct and conjugate addition have not been described. We wish to communicate our findings concerning reaction of ester enolates with 2-cyclohexen-1-one which, for the first time, demonstrate the importance of experimental parameters in partitioning direct and conjugate addition with stabilized carbanions.

At the outset of our work with ester enolate addition to enones, we had reason to believe that an equilibrium might be established between direct and conjugate addition products (eq 1).[4] Furthermore, we felt that, if kinetic addition occurs



(1)

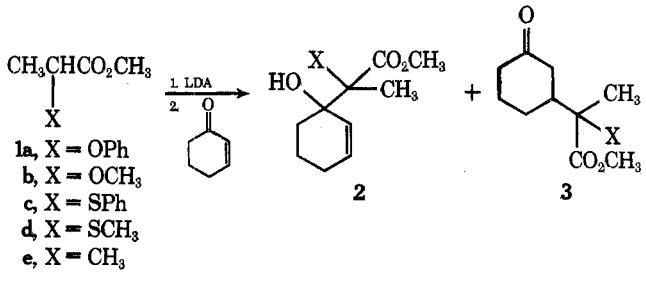
at the carbonyl carbon atom and equilibration leads to conjugate addition, then selective product formation might be possible by careful control of reaction temperature. As the following experiments demonstrate, this is indeed the case for reaction of ester enolates with 2-cyclohexen-1-one.

The ester enolate of methyl-2-phenoxypropionate (**1a**) is generated by addition of a tetrahydrofuran (THF) solution of **1a** to 1 equiv of lithium diisopropylamide (LDA), prepared in the usual manner[5] in THF at −78 °C. Addition of 1 equiv of 2-cyclohexen-1-one and stirring for 30 min, followed by careful quenching with saturated ammonium chloride solution at −78 °C, gives allylic alcohol **2a** (89% yield) and ketone **3a** (7%, bp 142–146 °C at 0.07 mm).[6] On the other hand, if the reaction mixture is warmed to 25 °C before quenching with water, ketone **3a** is the major reaction product (84% distilled yield). When a solution of pure **2a** (isolated as an oil by preparative, medium pressure, liquid chromatography) is added to 1 equiv of LDA at −78 °C and then is warmed to 25 °C, **3a** can be isolated in 91% yield.

Table I. Product Distribution as a Function of Reaction Temperature for Addition of Ester Enolates to 2-Cyclohexen-1-one

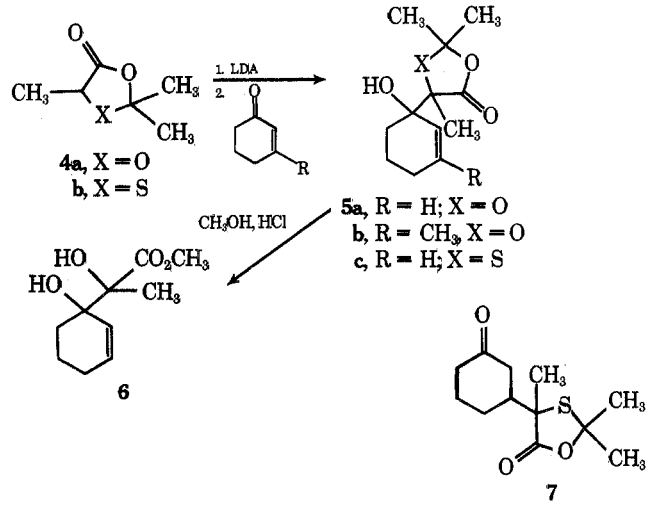
	−78 °C reaction		25 °C reaction	
Ester	% 1,2 addition	% 1,4 addition	% 1,2 addition	% 1,4 addition[a]
1a	88	8		84
1b	75	12	5	62[b]
1c		75		86
1d	63	7		85
1e	88	5	7	83

[a] Isolated yields; all other yields were determined by NMR and VPC analysis. Our limits of detectability were estimated to be ≤2%. [b] With shorter reaction time, yields were ~85–90%; however, much more 1,2-addition product was present.



We also have examined the reactivity of four other enolates derived from α-substituted methyl propionates and the results are presented in Table I. With ester enolates derived from **1b, 1d,** and **1e,** the 1,2-addition products **2b, 2d,** and **2e** were isolated and, as with **2a,** undergo conversion to **3b, 3d** and **3e,** respectively when treated with LDA at −78 °C and then warmed to 25 °C. Thus, kinetic addition is predominately (if not exclusively) taking place at the carbonyl carbon atom. Conjugate addition products arise by reversible formation of 1,2 adducts and subsequent 1,4 addition. With the ester enolate of methyl-2-thiophenoxypropionate (**1c**), however, equilibration occurs even at −78 °C (see Table I).

An interesting change in enolate reactivity was observed with the acetonide **4a.** Reaction with cyclohexenone at either −78 or 25 °C over prolonged reaction times gives only the product of 1,2 addition, **5a** (82% isolated yield, bp 93–95 °C



at 0.05 mm, chemical ionization mass spectrum *m/e* 227). Substitution of 3-methyl-2-cyclohexen-1-one for cyclohexenone gives only **5b,** isolated in 80% yield. When reaction of the ester enolate of **4a** with cyclohexenone is performed as usual, but is followed by addition of 1 equiv of 3-methylcyclohexenone with stirring for 1 h at 25 °C, only **5a** and unreacted 3-methylcyclohexenone are recovered. Clearly, with the enolate of **4a** and cyclohexenone, 1,2 addition is irreversible under these reaction conditions. With thiaacetonide **4b,** however, 1,2 addition is reversible and gives the product of conjugate addition **7** at 25 °C.

Thus, we have shown that, by simple structural modifications (e.g., **1a** and **1b** compared to **4a**) and careful control of reaction temperature, it is possible to direct ester enolates to either direct or conjugate addition with cyclohexenone. Furthermore, we note that the product of acetonide 1,2 addition, **5,** may be converted to the allylic pinacol **6** in nearly quantitative yield on treatment with methanolic hydrogen chloride, thus providing an exceptionally simple synthesis of this useful functionality.

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Arthur G. Schultz,* Ying K. Yee
Department of Chemistry, Cornell University
Ithaca, New York 14853
Received August 27, 1976

Prostaglandin Metabolites. Synthesis of E and F Urinary Metabolites

Summary: The synthesis of major urinary metabolites of E prostaglandins, 11α-hydroxy-9,15-dioxo-2,3,4,5,20-pentanor-19-carboxyprostanoic acid (**7a**), and F prostaglandins, 9α,11α-dihydroxy-15-oxo-2,3,4,5,20-pentanor-19-carboxyprostanoic acid δ-lactone (**8a**) is described.

Sir: The structure of the major human urinary metabolites of PGE_2[1] and $PGF_{2\alpha}$[2] has been determined by mass spectral analysis. The synthesis of those various metabolites have been reported.[3] We wish to report a highly efficient synthesis of one of the major human urinary metabolites of the PGE series, 11α-hydroxy-9,15-dioxo-2,3,5,20-pentanor-19-carboxyprostanoic acid (**7a**), and PGF series, 9α,11α-dihydoxy-15-oxo-2,3,4,5,20-pentanor-19-carboxyprostanoic acid δ-lactone (**8a**).[4]

The synthesis was designed to meet three important considerations: (1) the incorporation of deuterium or tritium could be easily accomplished, to enable synthesis of labeled metabolites; (2) the steps involved should be simple and efficient; (3) the intermediates should be flexible enough to allow for possible variations. The present synthesis meets those criteria and allows the synthesis of both E and F metabolites from a common precursor, **6a.**