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GLYCOLALDEHYDE MONOMER IN ORGANIC SYNTHESIS

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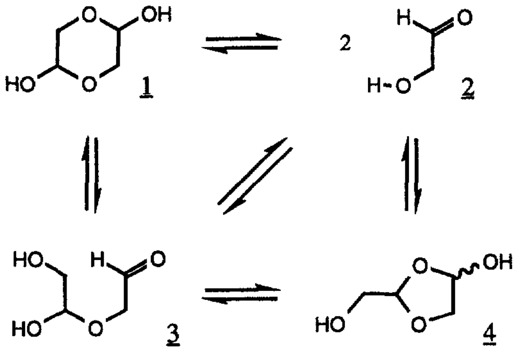
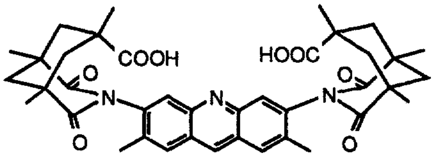
Summary : The lithium alkoxide of glycolaldehyde can be generated and trapped *in situ* by keto- and ester enolates to yield the corresponding keto-epoxides and hydroxy lactones respectively.

Despite its obvious potential in organic synthesis, the smallest hydroxy aldehyde, glycolaldehyde, has so far eluded synthetic usage in its unprotected form, the reason being that solid glycolaldehyde exists as a dimer 1 whose dissociation to the monomer 2 is not straight forward but involves, probably, other dimeric intermediates. As early as 1939 Bell[1] proposed linear structure 3 as the dissociation intermediate, while shortly afterwards Spath[2] reported the detection of 1,3-dioxolane dimer 4.[3] It was much later, however, before the co-existence of 1, 2 and 4 in solution was observed by Stassinopoulou[4], employing NMR spectroscopy. Thus the spectrum of solid glycolaldehyde in dimethyl sulfoxide displays chemical shifts and coupling constants consistent with a mixture of 1, 2 and 4. A recent development is the report by Rebeck, Jr.,[5] of an extremely effective catalyst, diacid 5 which remarkably catalyses the dissociation of 1 to 2, probably via the straight chain dimer 3.

Scheme I





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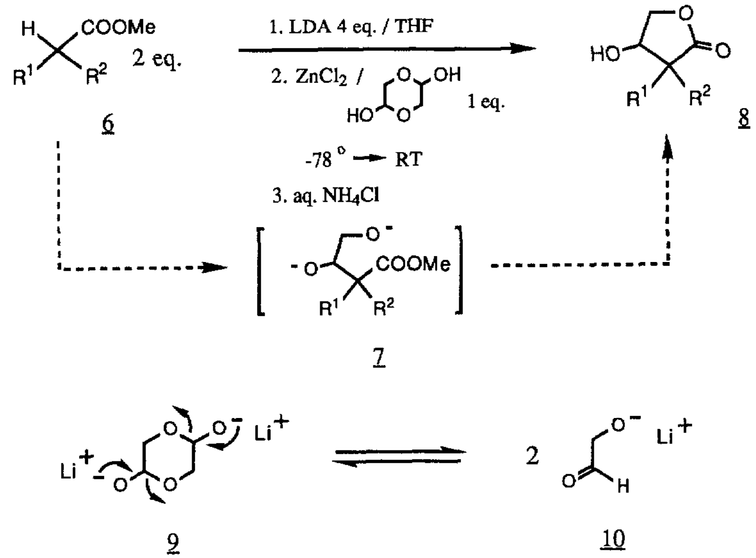
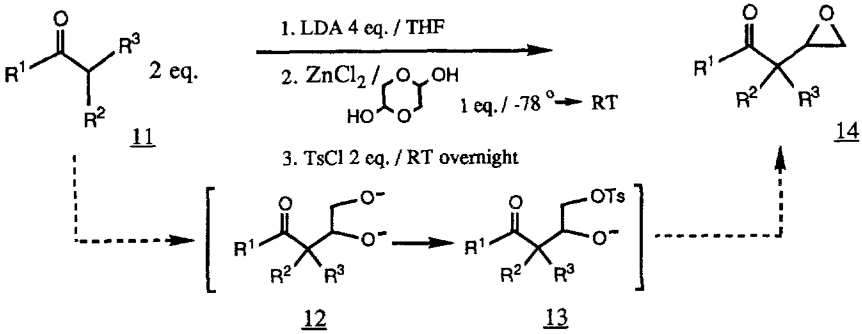
It was envisioned that, under suitable conditions with sufficiently high concentrations of monomer 2, it would be feasible to trap the molecule in the presence of nucleophiles. The benefit of a successful endeavour is quite evident: it would allow the direct preparation of useful compounds from commercially available solid glycolaldehyde dimer 1. Here we report such trapping of monomer 2 by ester- and keto enolates.

A solution of ester 6 [2 equivalents] in THF was added to a pre-formed solution of lithium diisopropylamide [LDA, 4 eq.] in the same solvent at -78° and the mixture left to stir at 0° for 30 minutes, then cooled to -78°. A solution of zinc chloride [2 eq. in THF] was then added, followed immediately by solid commercial glycolaldehyde[6] [1 eq.], and the reaction mixture then stirred overnight. Finally, hydroxy lactone 8 was isolated after saturated aqueous ammonium chloride work-up, as summarized in **Scheme II**. The stoichiometry indicated in the **Scheme** is based on our supposition that dilithio derivative 9 [derived from 1] would, to a certain extent, break down in THF solution to 10 which would then spontaneously react with the lithium ester enolate. Experimental results are shown in **Table**.

Scheme II

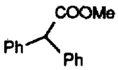
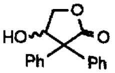
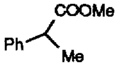
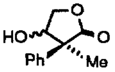
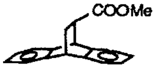
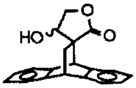
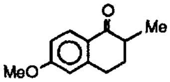
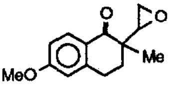
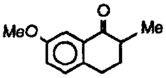
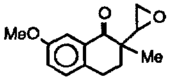
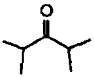
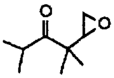
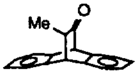
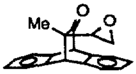


Scheme III



The reaction applies also to keto enolates, in which case the intermediate keto dialkoxide 12 can either be protonated to give the corresponding keto-diol, or converted, in one-pot, to epoxide 14 by the addition of an equimolar amount of p-toluenesulfonyl chloride as shown in **Scheme III** [see **Table**].[7]

Table

Starting material		Product		% conversion of starting material	% Yield[a]
	6a		8a	57	63
	6b		8b	44	65[b]
	6c		8c	56	77[c]
	11a		14a	60	46[d]
	11b		14b	56	43[d]
	11c		14c	-[e]	49
	11d		14d	63	56[d]

[a] Purified yield, calculated from reacted starting material.

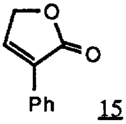
[b] Two separable isomers, ratio 1 : 1 [silica gel, methylene chloride as eluant].

[c] Two separable isomers, ratio 1 : 2 [silica gel, methylene chloride as eluant].

[d] Only one epoxide obtained.

[e] Starting material could not be recovered due to low boiling point ; reported yield [49%] calculated from total starting material employed.

It is evident from the results obtained that under the conditions employed the concentration of monomeric alkoxy aldehyde 10 is high enough and can be usefully trapped. Solid glycolaldehyde dimer 1 can therefore be regarded as a good source of monomer 2, upon which simple manipulations can selectively yield hydroxy lactone 8 or epoxy ketone 14. To improve the extent of starting material conversion and total yields, various reaction conditions have been investigated including the use of excess 1, LDA, and prolonged reaction times, none of which have been found to be superior to that described above. Also, the reaction appears to perform better with α-disubstituted esters and ketones such as those in entries 6 and 11. Esters and ketones with two α-hydrogen atoms give complex reactions and several products are formed. For example, when subjected to the above reaction conditions, methyl phenylacetate gave butenolide 15 and allyl alcohol 16 [both apparently arising from dehydration of the intermediate diol] in 11% and 7% yields respectively. Despite this drawback, the trapping of the glycolaldehyde dimer dissociation product is nevertheless very useful when the ready availability of 1 and the simple reaction procedures are taken into consideration. For example, flash vacuum pyrolysis[8] of 8c quantitatively gave [±]-tulipalin B 17, the skin sensitizer methylene-γ-butyrolactone isolated from Tulipa gesneriana L.[9] Thus 17 was obtained in two steps from anthracene-methyl acrylate adduct 6c in 43% overall yield.



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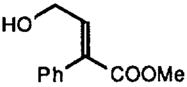

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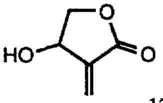

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