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A FACILE SYNTHESIS OF 4-OXO CARBOXYLIC ACIDS FROM γ-BUTYROLACTONE.

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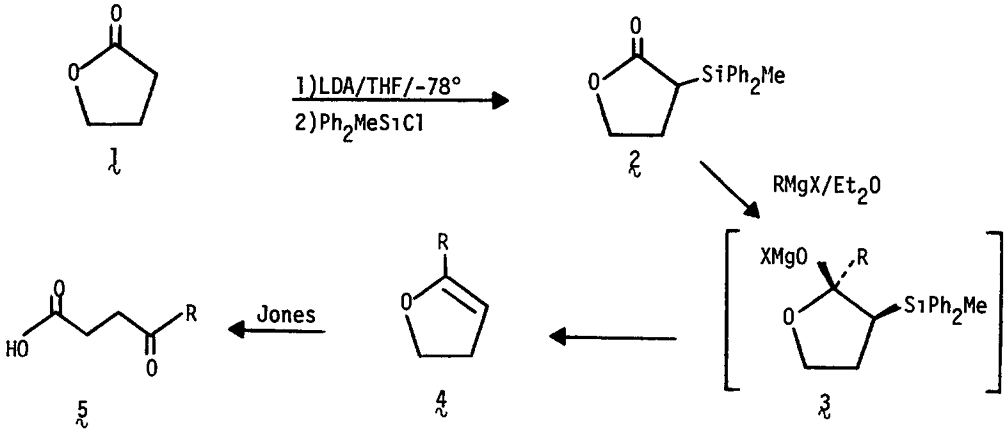
Summary: An efficient, high-yield, three-step preparation of 4-oxo carboxylic acids from γ-butyrolactone via silylation and reaction with a Grignard reagent is presented.

The preparation of 4-oxo carboxylic acids is of interest since these compounds are, among other things, important precursors to substituted γ-butyrolactones via the γ-hydroxy acid.[2] We report, herein on the efficient conversion of γ-butyrolactone to 4-oxo carboxylic acids as outlined in Scheme 1. The key factors to the success of this synthetic approach are the C-silylation of the lithium enolate of γ-butyrolactone[3] and the reaction of the α-silylated lactone with a Grignard reagent.[4]

Clean C-silylation of the lithium enolate of γ-butyrolactone is accomplished by quenching with diphenylmethylchlorosilane[3,5] to give **2** in 94.9% isolated yield. Treatment of **2** with an excess of a Grignard reagent in ether followed by Jones oxidation of the crude material, extraction with sodium hydroxide solution and acidification of the aqueous layer gives the 4-oxo acid in good yield. The results are shown in Table I. The reaction seems to be rather general although no reaction was observed with isopropylmagnesium bromide and tert-butylmagnesium chloride gave reduction rather than addition to the carbonyl, yielding succinic acid as the ultimate product.

We propose that the Grignard reagent adds to the carbonyl preferentially from the least hindered side to give cis-β-alkoxysilane, **3** as an intermediate. Intermediate **3** is ideally arranged to lose diphenylmethylsiloxide in a cis manner[6] forming the dihydrofuran,[7] **4**, which is then oxidized to the keto acid, **5**.



The preparation of 4-oxohexanoic acid is representative of the procedure. A dry, 250 mL, standard apparatus, under a nitrogen atmosphere was charged with 25 mL of ether and 2.82 g (10 mmol) of 2. With this solution at rt, 30.0 mL of a 1.0 M ethylmagnesium bromide solution in ether (30 mmol) was added slowly. The reaction mixture was stirred at rt for 24 h, cautiously hydrolyzed by the addition of water (10 mL) at 0°C, diluted with benzene (10 mL) and titrated with chromic acid solution. The organic layer was extracted with 3N sodium hydroxide (10 mL) and the aqueous layer acidified pH 3 with 1.5 N hydrochloric acid. The aqueous layer was then extracted with ether (2 x 25 mL), dried and concentrated to give the crude keto acid which was crystallized from hexane to give 0.94 g (72.3%) of 4-oxohexanoic acid.

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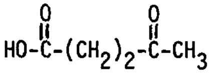
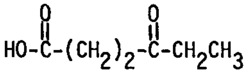
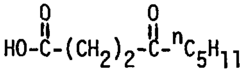
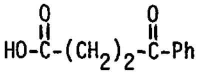
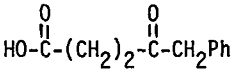
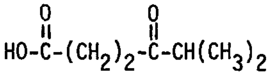
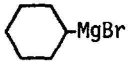
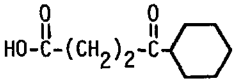
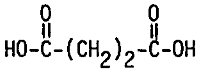
Table I· Synthesis of 4-oxo acids from α-(diphenylmethylsilyl)-γ-butyrolactone, **2**.

Grignard Reagent	γ-keto acid (mp)	% Yield
CH_3MgI	 $HO-\overset{O}{\overset{\|}{C}}-(CH_2)_2-\overset{O}{\overset{\|}{C}}-CH_3$ (32-34)[a]	71.2
CH_3CH_2MgBr	 $HO-\overset{O}{\overset{\|}{C}}-(CH_2)_2-\overset{O}{\overset{\|}{C}}-CH_2CH_3$ (39-40)[b]	73.2
$CH_3CH_2CH_2CH_2CH_2MgBr$	 $HO-\overset{O}{\overset{\|}{C}}-(CH_2)_2-\overset{O}{\overset{\|}{C}}-{}^{n}C_5H_{11}$ (69-70)[c]	82.6
PhMgBr	 $HO-\overset{O}{\overset{\|}{C}}-(CH_2)_2-\overset{O}{\overset{\|}{C}}-Ph$ (115-116)[d]	75.1
$PhCH_2MgCl$	 $HO-\overset{O}{\overset{\|}{C}}-(CH_2)_2-\overset{O}{\overset{\|}{C}}-CH_2Ph$ (54-55)[e]	77.7
$(CH_3)_2CHMgBr$	 $HO-\overset{O}{\overset{\|}{C}}-(CH_2)_2-\overset{O}{\overset{\|}{C}}-CH(CH_3)_2$	0
		50
$(CH_3)_3CMgCl$	 $HO-\overset{O}{\overset{\|}{C}}-(CH_2)_2-\overset{O}{\overset{\|}{C}}-OH$ (185-187)[f]	75.0

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a. lit.[8] mp 33-35°; b. lit.[9] mp 40°; c. lit.[10] mp 70-71°,

d. lit.[11] 115-115.5°; e. lit.[12] mp 55-56°, f. lit.[13] 185°.

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