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Enantioselective synthesis of δ-ketobutanolides from (L)-glutamic acid via organomanganese reagents †

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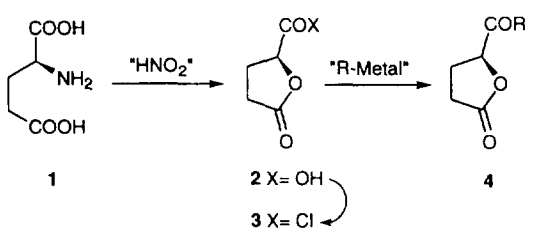
Abstract: Various optically active δ-ketobutanolides were easily prepared in good yields, with an excellent enantiomeric purity, by acylation of organomanganese reagents with the butyrolactone acid chloride **3** prepared from natural (L)-glutamic acid. The reaction takes place in THF under mild conditions (−10°C, 3h or 3% CuCl, −30°C, 20 min.). © 1997 Elsevier Science Ltd

δ-Functionalized γ-lactones are important building blocks in natural product synthesis. They are also frequently encountered as structural subunits in some biologically active products.[2] Thus, optically active δ-ketobutanolides have been employed as key intermediates to prepare various natural products[3–5] especially δ-hydroxybutanolides.[6] As an example, they have been recently used to synthesize acetogenins of Annonaceae, a new class of compounds actively studied for their biological properties.[7] One of the simplest strategies described to prepare δ-ketobutanolides involves (L)-glutamic acid as starting product (Scheme 1).[4,5]



Scheme 1

The key step of this procedure is the acylation of an organometallic with the carboxylic acid chloride **3**. Organocadmium[4] as well as organocuprates and organomagnesium[5] reagents were used. Unfortunately, organocadmiums and cuprates gave very often poor yields,[4,5] whereas Grignard reagents require reaction conditions which are not convenient for large scale preparations (low temperature and low concentration of the reactants), especially with the long-chain alkylmagnesium reagents.[5]

Previously, we have shown that the acylation of organomanganese bromides and chlorides allows the preparation of a vast array of ketones in high yields under mild conditions. This reaction is highly chemoselective since even a keto group is tolerated.[8,9] On the other hand, we have recently reported that organomanganese reagents cleanly react with various enantiomericaly pure acyclic α-acyloxy carboxylic acid chlorides to give the corresponding α-acyloxyketones without isomerization of the α-stereogenic center.[10] Now, we describe the preparation of various optically-active δ-ketobutanolides **4** by acylation of organomanganese reagents according to the following scheme (Table 1).

† Organomanganese Reagents Part XXXIV. For Part XXXIII see ref [1].

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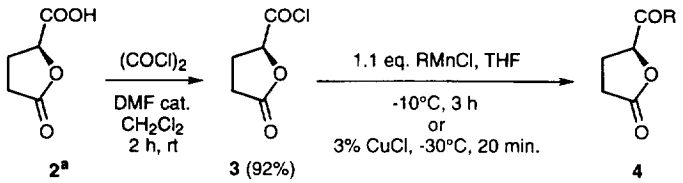
Table 1. Preparation of δ-ketobutanolides **4** by acylation of organomanganese reagents



2[a] **3** (92%) **4**

Entry	R	% Yield[b]	ee (%)[c]
1	n-C_4H_9	90[d]	98.0
2	n-$C_{12}H_{25}$	92[d]	98.2
3	i-C_3H_7	65[e]	96.0
4	t-C_4H_9	85[e]	97.2
5	C_6H_5	80[e,f]	97.3
6	n-$C_5H_{11}C{\equiv}C$	58	-[g]

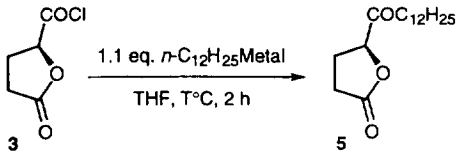
a/ For the preparation of **2** from (*L*) glutamic acid see ref. 10. **b/** Yield of isolated product. **c/** ee were determined by GC with a chiral Cydex-β column (SGE, 25QC3/CYDEX-B 0.25, 25m, 0.25μ). **d/** -10°C, 3h. **e/** 3% CuCl, -30°C, 20 min. **f/** Yield was improved by adding RMnCl to **3** in 30 min., normal addition only gave 67% yield. **g/** ee was not determined.

Glutamic acid **1** was deaminated with aqueous nitrous acid ($NaNO_2$–H_2SO_4) to give the lactone acid **2**.[11] Carboxylic acid chloride **3** was then obtained by treating **2** with oxalyl chloride in the presence of DMF as catalyst. As shown in Table 1, the acylation of organomanganese chloride reagents with **3** takes place in THF under mild conditions and affords δ-ketobutanolides **4** in excellent yields and high enantiomeric purities. When R=Ph, *t*-Bu and *i*-Pr, the addition of a catalytic amount of copper chloride (3%) is essential to obtain good yields of ketones **4** (Table 1, entries 3 to 5). Such a beneficial influence of copper chloride as catalyst has already been reported for the acylation of aryl as well as *s*- or *t*-alkylmanganese halides in THF.[7] In the absence of copper chloride the reaction times are longer and the yields are lower.

This new method of preparation of δ-ketobutanolides compares very favorably to the acylation of Grignard reagents previously described.[5] Indeed, it gives higher yields and is easier to carry out since the results are clearly less dependent on both the temperature and the concentration of the reactants (Table 2, entries 1 to 4). The difference is greatest when the reaction is performed on a large scale. As an example, on a 20 g scale the yield of ketone **5** dropped to 50% by using dodecylmagnesium bromide at −78°C whereas the corresponding organomanganese reagent gave a 76% yield at 0°C (Table 2, entries 5 and 6). In addition, it should be noted that at low temperature (−78°C) the use of Grignard reagents is often tedious since they can precipitate and lead to unreproducible results. This drawback frequently occurs with RMgX having a large R group (>C_7).

During our investigations, we have also observed that the preparation of δ-ketobutanolides from alkenylmagnesium halides is especially delicate.[12] Thus, the acylation of 2-methyl propenylmagnesium bromide only gave 45% yield of ketone **6** (Table 3, entry 1) under the best conditions (0.2M, −78°C). Comparatively, the corresponding organomanganese reagent gave a much higher yield at 0°C (84%, entry 2).

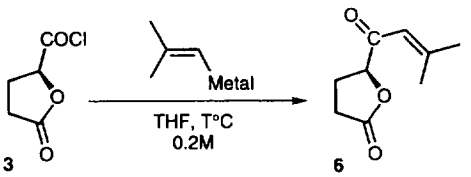
Table 2. Preparation of δ-ketobutanolide **5** by acylation dodecylmagnesium bromide and dodecylmanganese chloride



Entry	*n*-$C_{12}H_{25}$Metal	Concentration[a]	T°C	Yield (%)
a/ From 7g of **3**				
1	*n*-$C_{12}H_{25}MgBr$	0.2 M	-78°C	80[b]
2	"	0.8 M	-78°C	25[b]
3	"	0.8 M	0°C	> 3[c]
4	*n*-$C_{12}H_{25}MnCl$	0.8 M	0°C	92[b]
b/ From 20g of **3**				
5	*n*-$C_{12}H_{25}MgBr$	0.4M	-78°C	50[b]
6	*n*-$C_{12}H_{25}MnCl$	0.4 M	0°C	76[b]

a/ Concentration of the reactants in the reaction mixture. **b/** Yield of isolated product. **c/** GC yield.

Table 3. Preparation of Δ-ketobutanolide **6** by acylation of 2-methylpropenylmagnesium bromide and 2-methylpropenylmanganese chloride



Entry	Me_2C=CH-Metal	T°C	% Yield[a]	% ee
1	Me_2C=CHMgBr	-78	45	97.8
2	Me_2C=CHMnCl[b]	-10	84	98.0

a/ Yield of isolated product. **b/** 3% CuCl, -30°C, 20 min.

In conclusion, we have shown that optically active δ-ketobutanolides, which are interesting intermediates in the synthesis of biologically active natural products, are readily prepared in high yields with an excellent enantiomeric purity from commercially available (L)-glutamic acid. The key step of this procedure, the acylation of organomanganese reagents with the butyrolactone acid chloride **3**, is of real preparative interest. It is much easier to carry out than the acylation of Grignard reagents previously described, especially on a large scale (concentration and temperature), and gives higher yields.

General procedures

Acylation of RMnCl with butyrolactone acid chloride 3 (Table 1; entries 1, 2 and 6)

A suspension of anhydrous $MnCl_2$ (55 mmoles) and LiCl (100 mmoles) in THF (50 mL) was stirred at room temperature until dissolution occurs. Next, RMgCl/THF (53 mmoles) was added at −10°C and the resulting solution was stirred for 15 min. A solution of butyrolactone acid chloride **3** (50 mmoles) in THF (15 mL) was then added dropwise at −10°C. After stirring for 3 h at room temperature, the reaction mixture was hydrolyzed at −10°C with a 1N HCl aqueous solution (60 mL). After decantation, the aqueous layer was extracted twice with ether (80 mL) and the combined organic layers were dried over magnesium sulfate. The solvents were then removed under vacuum and the ketobutyrolactone **4** was isolated by distillation or by flash chromatography on a silicagel column (230–400 mesh).

Cu-Catalyzed acylation of RMnCl with butyrolactone acid chloride 3 (Table 1, entries 3 to 5; Table 3, entry 2)

To the solution of RMnCl prepared according to the previous procedure, copper chloride (3%) and carboxylic acid chloride **3** were succesively added at −30°C. Stirring was continued for 20 min at −30°C then the reaction mixture was hydrolyzed and treated as above.

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12. A similar observation has already been reported in the case of CH_2=CHMgCl (see ref[5]).

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