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A FACILE AND STEREOSELECTIVE SYNTHESIS OF α-METHYLENE-γ-BUTYROLACTONE BY MEANS OF CHROMIUM(II) REAGENT

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Treatment of ethyl α-(bromomethyl)acrylate with Cr(II) reagent derived from $CrCl_3$ and $LiAlH_4$ produces allylic chromium species which add to aldehydes efficiently to give α-methylene-γ-butyrolactones stereoselectively.

Recently much attention have been paid on marine natural products such as cladiellolide$^{1)}$ and lobolide$^{2)}$ because of their high biological activities. The α-methylene-γ-butyrolactone structural unit has been suggested to play an important role in the mechanism of action of these physiologically active compounds. Many methods are now available for introduction of the exo-methylene unit into a γ-lactone ring,$^{3)}$ but a more direct strategy would be preferable. Here we wish to describe a new, facile method for the synthesis of α-methylene-γ-butyrolactones based on 2-carboethoxyallylation$^{4)}$ of carbonyl compounds.

Previously reported reactions$^{5)}$ of allylic chromium reagent with carbonyl compounds provided homoallylic alcohols with high degree of stereo- and chemoselectivity. Application of this procedure to functionalized allylic chromium reagent has provided us with a simple route to α-methylene-γ-butyrolactone. Typical experimental procedure is as follows. Lithium aluminium hydride (76 mg, 2.0 mmol) was added portionwise to a suspension of $CrCl_3$ (0.63 g, 4.0 mmol) in THF (5 ml) at 0 °C under an argon atmosphere. Immediate gas evolution occurred with darkening of the initial purple color which finally turned dark brown. After the gas evolution had ceased, the reaction mixture was stirred for an additional 15 min at 25 °C. A solution of benzaldehyde (0.11 g, 1.0 mmol) in THF (5 ml) was added in one portion, then a solution of ethyl α-(bromomethyl)-acrylate$^{6)}$ (0.38 g, 2.0 mmol) in THF (5 ml) was added dropwise over 10 min. The

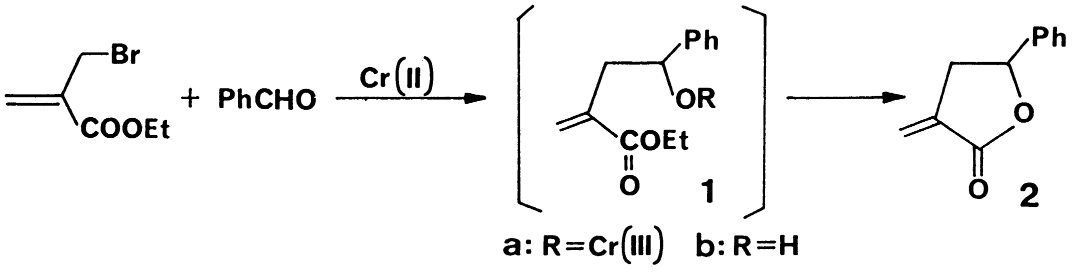
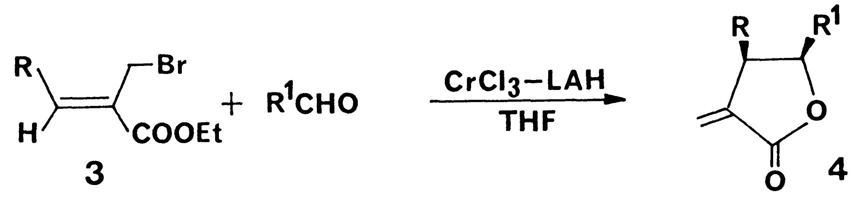


Table 1. Synthesis of α-methylene-γ-butyrolactones

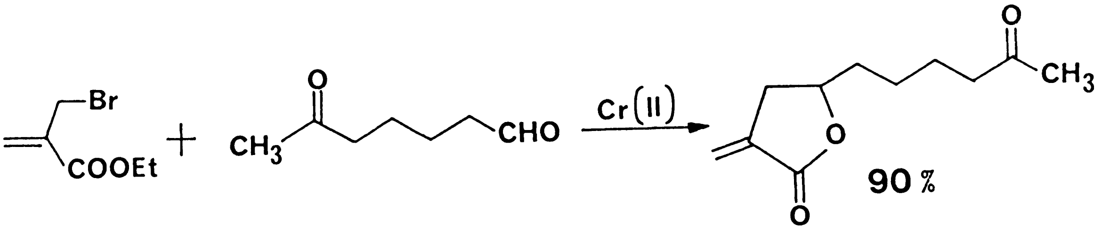


Entry	Allylic bromide R	Aldehyde R^1	Yield[a] of 4 %
1	H (**3a**)	Ph	94
2	H (**3a**)	n-C_4H_9	82
3	H (**3a**)	$CH_3CH=CH$	46
4	H (**3a**)	i-C_4H_9	80
5	H (**3a**)	$CH_2=CH(CH_2)_9CH_2$	70
6	n-C_4H_9 (**3b**)	Ph	86[b]
7	n-C_4H_9 (**3b**)	n-C_4H_9	75[b]
8	n-C_4H_9 (**3b**)	$CH_3CH=CH$	52[b,c]

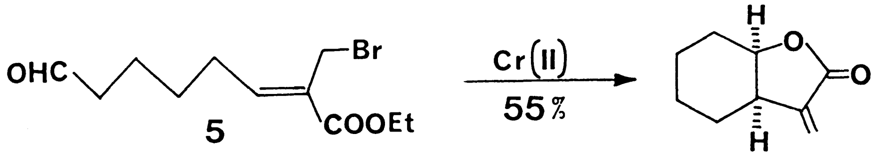
a) Isolated yields. b) Only cis isomer was obtained. The trans isomer could not be observed in the crude product. c) See Ref. 7.

resulting mixture was stirred for 3 h at 25 °C and poured into ice-cold water. Workup (Et_2O, 1.0 mol dm^{-3} HCl) and purification by thin layer chromatography on silica gel gave α-methylene-γ-phenyl-γ-butyrolactone **2** (0.16 g) in 94% yield as a colorless oil.[4c]

Representative results are summarized in Table 1. General features of the reaction are as follows: (1) The use of the chromium(II) reagent derived from $CrCl_3$ and $LiAlH_4$ is essential for the direct formation of α-methylene-γ-butyrolactone. Meanwhile, treatment of PhCHO and ethyl α-(bromomethyl)acrylate with commercially available $CrCl_2$[8] provided γ-hydroxy ester **1b** in 61% yield after aqueous workup. The α-methylene-γ-butyrolactone **2** was not detected in the crude product. The coexsiting Lewis acid such as $AlHCl_2$ might play an important role for the cyclization in the case of the former reagent. (2) With α,β-unsaturated aldehyde, the reaction proceeds exclusively in 1,2-fashion (Entry 3 and 8). (3) Chromium(II) mediated reaction of **3b** with valeraldehyde gave cis-β,γ-dibutyl-α-methylene-γ-butyrolactone as a single product.[9] The E isomer of **3b**[10] also provided cis-lactone in 70% yield exclusively under the same reaction conditions. Thus, the stereochemical integrity of the α-(bromomethyl)acrylate **3b** and its E isomer was lost completely.[11] In contrast, treatment of a mixture of **3b** and valeraldehyde with zinc according to the reported procedure[13] gave a mixture of cis- and trans-dibutyl compound (cis/trans = 1/1, 50% yield). (4) Ketones react sluggishly, thus the chemoselective carbonyl addition was achieved as shown below.



The new method was successfully applied to the synthesis of α-methylene-γ-butyrolactone fused to six-membered carbocyclic ring. Treatment of 5 with Cr(II) reagent gave cis-fused lactone exclusively.[14,15]



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6) Prepared from diethyl bis(hydroxymethyl)malonate according to the reported procedure. A. F. Ferris, J. Org. Chem., 20, 780 (1955).
7) IR (neat) 2910, 1755, 1268, 1113, 965 cm^{-1}; NMR (CCl_4) δ0.75-1.06 (m, 3H), 1.06-1.63 (m, 6H), 1.75 (d, J = 6.3 Hz, 3H), 2.70-3.09 (m, 1H), 4.75 (dd,

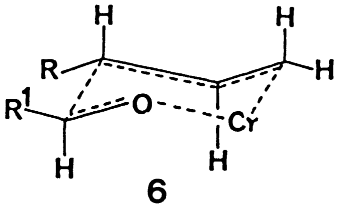
J = 7.2, 7.2 Hz, 1H), 5.30 (dd, *J* = 7.2, 16.0 Hz, 1H), 5.34 (d, *J* = 3.0 Hz, 1H), 5.75 (dq, *J* = 16.0, 6.3 Hz, 1H), 6.05 (d, *J* = 3.0 Hz, 1H). Found: C, 74.12; H, 9.60%. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34%.

8) Anhydrous chromium(II) chloride was purchased from ROC/RIC Corp. (507-519 Main Street, Belleville, NJ 07109, U. S. A. or Aldrich Chemical Co. and was used without further purifications.

9) cis-β,γ-Dibutyl-α-methylene-γ-butyrolactone: NMR ($CDCl_3$) δ0.80-1.06 (m, 6H), 1.10-1.73 (m, 12H), 2.87-3.06 (m, 1H), 4.43-4.59 (m, 1H), 5.54 (d, *J* = 2.5 Hz, 1H), 6.22 (d, *J* = 2.5 Hz, 1H). trans-Isomer: NMR ($CDCl_3$) δ0.80-1.06 (m, 6H), 1.10-1.73 (m, 12H), 2.59-2.76 (m, 1H), 4.14-4.29 (m, 1H), 5.61 (d, *J* = 2.6 Hz, 1H), 6.29 (d, *J* = 2.6 Hz, 1H). The assignment was based on the comparison of the spectral data with those of cis- and trans-β,γ-dihexyl-α-methylene-γ-butyrolactones.4d)

10) A mixture of E and Z-isomer was obtained according to the following literature (M. F. Semmelhack, J. C. Tomesch, M. Czarmy, and S. Boettger, J. Org. Chem., 43, 1259 (1978)). The E and Z-isomer were carefully separated by silica gel column chromatography.

11) The threo selectivity observed on the reaction of allylchromium species with aldehydes is explained reasonably by a chair form transition state **6**.5) On the other hand, the cis selective reactions described here may be understood by the anticipated coordination of oxygen of ester group to chromium(III) and accordingly by favouring noncyclic transition state12) depicted below. The chelate formation between aldehyde oxygen and Cr(III) may not be important. The coexisting Lewis acid such as $AlHCl_2$ might also play a critical role for the stereoselective formation of cis products.



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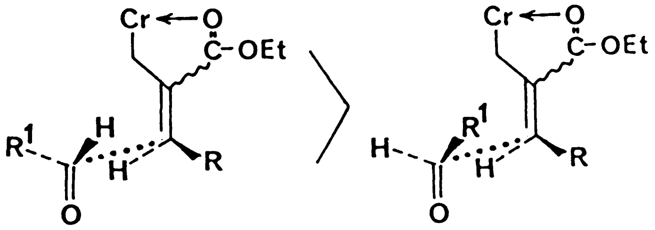

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13) The reaction was performed according to the literature4a) with some modifications. The substrate **3b** was used instead of **3a** and the reaction mixture was heated at reflux in THF for 3 h.

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