Registry No. $Mo_2(SC_6H_2Me_3)_6$, 86350-27-8; 1,2-Mo_2(S-*t*-Bu)$_2$-$(NMe_2)_4$, 83312-38-3.

Supplementary Material Available: Table of atomic coordinates for the $Mo_2(SC_6H_2Me_3)_6$ molecule (1 page). Ordering information is given on any current masthead page.

Stereochemical Control of Yeast Reductions. 1. Asymmetric Synthesis of L-Carnitine

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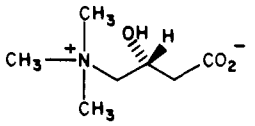
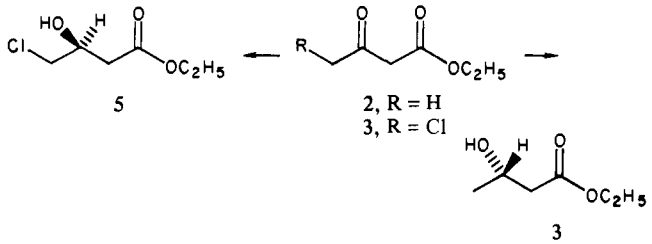
L-Carnitine (**1**) plays an important role in the human metabolism and transport of long-chain fatty acids.[1] Because D-carnitine



1

is a competitive inhibitor of L-carnitine acyl transferases[2] and can deplete the L-carnitine level of heart tissue, L-carnitine has been recommended for replacement therapy.[3] We herein describe an efficient chemomicrobiological synthesis of L-carnitine, which obviates the tedious expensive resolution methods that are currently being used in its chemical synthesis.[4] The salient feature of this approach resides in our ability to direct the sterochemical course of yeast reduction of β-keto esters.

Ethyl acetoacetate (**2**) is reduced by bakers' yeast (*Saccharomyces cerevisiae*) to give ethyl (*S*)-(+)-3-hydroxybutanoate[5] (**3**) of high optical purity. Hence, we envisaged that ethyl γ-chloroacetoacetate (**4**) perhaps would be similarly reduced to yield ethyl (*R*)-4-chloro-3-hydroxybutanoate, which could then be easily transformed into L-carnitine by known methodology.[6] However, when **4** was exposed to bakers' yeast, ethyl (*S*)-4-chloro-3-hydroxybutanoate[7a] (**5**), $[\alpha]^{23}_D$ −11.7° (*c* 5.75, $CHCl_3$) (ee = 55%),[7b] was preferentially formed.



5 **2**, R = H; **3**, R = Cl

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It is generally assumed that the stereoselectivity of yeast reductions of acyclic ketones may be predicted by the Prelog rule.[8-11]

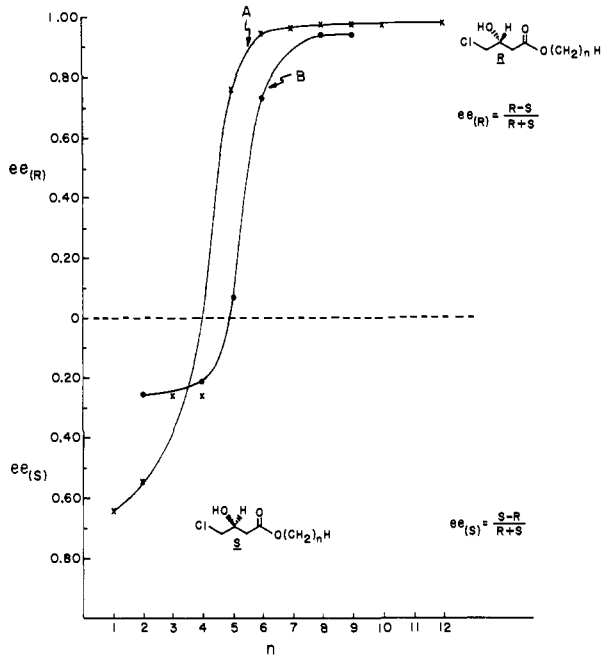

Figure 1. Plot of enantiomeric excess (ee) vs. the size of ester grouping: (A) Red Star bakers' yeast (4 g), tap water (20 mL), 23 °C; γ-chloroacetoacetic esters (0.91 mmol); (B) Red Star bakers' yeast (12 g), tap water (20 mL), 23 °C; γ-chloroacetoacetic esters (2.7 mmol). Usual workup after 48 h.

However, the applicability of the Prelog rule to yeast reduction of β-keto carbonyl derivatives has not been closely examined. We noted that while ethyl acetoacetate[12] and acetoacetic acid[13] were reduced predominantly to their *S* isomers, ethyl β-ketovalerate[14] (**6**) and caproic[13] (**7**), caprylic[13] (**8**), and β-keto-6-heptenoic[15] (**9**) acids were all preferentially converted into their respective *R* isomers. Consequently, if the stereochemistry of yeast reduction of γ-chloroacetoacetic esters could also be altered, i.e., from *S* → *R*, by modifying the size of the ester grouping, (*R*)-γ-chloro-β-hydroxybutyrate could then be obtained for L-carnitine synthesis.

To test our hypothesis, we synthesized a homologous series of γ-chloroacetoacetic esters[16] ranging from C_1 to C_{16} and exposed them to bakers' yeast (Figure 1). Although there was no significant difference in the rates of yeast reduction of γ-chloroacetoacetic esters containing one–eight carbons (n = 1–8), there was a drastic decrease in the reduction rate for the C_{12} ester, which resulted in low product yield. No reduction was observed for the C_{16} ester. More importantly, contrary to the current view,[17] there was indeed a dramatic shift in the stereochemistry of the carbinols formed as the size of the ester grouping is enlarged (Figure 1).

If these β-keto esters are reduced by a single oxidoreductase, this enzyme is able to interact with both faces of the carbonyl group to form two competing *R* and *S* transition states, one of which is more favored than the other. A second possibility is that yeast contains more than one oxidoreductase, which generates carbinols of opposite configurations but at different rates.

Since the optical purities of the various esters change with concentration (curve B, Figure 1), this demonstrates[18] that bakers' yeast contains at least two oxidoreductases producing γ-chloro-

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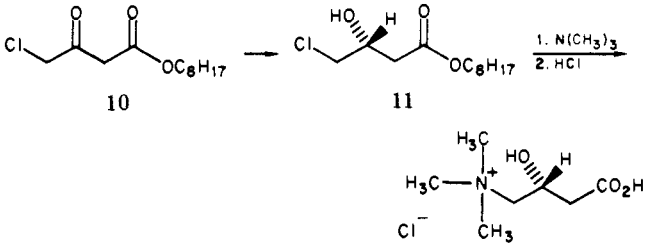
β-hydroxybutanoates of opposite configurations at different rates.

The ready availability of (*R*)-γ-chloro-β-hydroxybutyrate of high configurational purity allows us to complete the asymmetric synthesis of L-carnitine. This was accomplished by reaction of octyl (*R*)-γ-chloro-β-hydroxybutyrate (**11**) with an excess of trimethylamine in ethanol at 80 °C, followed by hydrolysis with 3 N HCl for 2 h. Crystallization from ethanol–acetone afforded L-carnitine chloride in 45% overall yield: mp 142 °C dec; $[\alpha]^{23}_D$ −22.9° (*c* 4.0, H_2O) (lit.[19] $[\alpha]_D$ −23.7°).



The feasibility of regulating the stereochemical course of yeast reduction by designing substrates with significant differences in *V* and/or *K* values for the competing enzymes provides a general method for the preparation of β-hydroxybutyric esters of either *S* or *R* configurations. Studies on the isolation and properties of the oxidoreductases are in progress.

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Supplementary Material Available: Detailed experimental section (6 pages). Ordering information is given on any current masthead page.

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Formation of a Stable (η^2-C,C) Ketene Compound $(C_5H_5)Fe(CO)_2(CH_2CO)^+PF_6^-$ by Carbonylation of an Iron–Methylidene Complex. A Novel Entry into CO-Derived C_2 Chemistry

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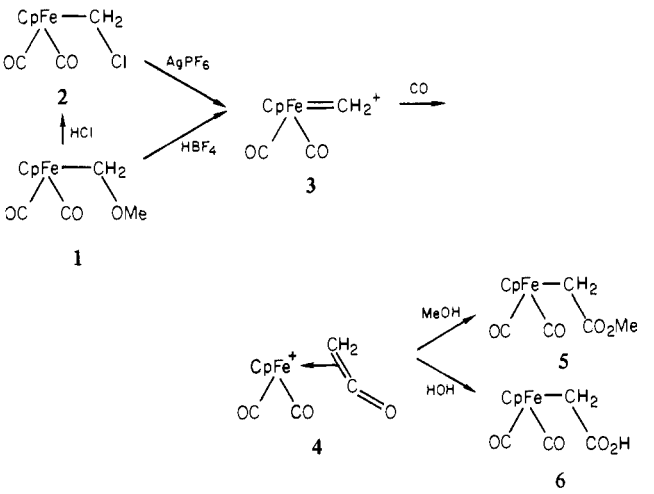
Ligated ketene obtained by carbonylating a methylidene ligand represents a plausible intermediate in homogeneous carbon monoxide fixation, and indeed postulated mechanisms for homogeneous analogues of the Fischer–Tropsch synthesis[1] sometimes incorporate μ-[η^2-C,C] ketene complexes MCH_2COM.[2] Ketenyl/carbonylmethylidene (CRCO)[3] and ketenylidene/carbonylmethylidyne (CCO)[4] ligands additionally result from transferring CO to the requisite C_1 ligand. Very little is known, however, about the carbonylation of terminal methylidene ligands,[5] although (η^2-C,O) ketene complexes of Cp_2Ti and Zr[6] have been obtained by other procedures. More is known about substituted ketenes: uncoordinated species can be generated by carbonylating their called-for carbene complexes,[7] or a number of stable diphenylketene complexes can be prepared by its direct ligation.[8] Of particular relevance to the present study is Herrmann's observation that $Cp(CO)_2Mn(CPh_2)$ converts to its stable (η^2-C,C) diphenylketene complex[9a] under CO pressure,[9b] possibly via intermolecular carbene transfer to a metal carbonyl. He found no evidence for either CO addition to the ligated carbene or the postulated carbene-CO migratory insertion[5,7a,10] in studies with the analogous anthronylketene complex.

Scheme I



We now report that (1) an electrophilic methylidene ligand picks up exogenous CO under extremely mild conditions, giving a stable (η^2-C,C) ketene complex, and (2) this ketene ligand transforms into its carbomethoxymethyl group, representing a novel synthesis of a C_2 alkyl ligand from carbon monoxide.

The extremely reactive methylidene salt $FpCH_2^+PF_6^-$ (**3**),[11] Fp = $Cp(CO)_2Fe$, affords the known carbomethoxymethyl

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