Tetrahedron: Asymmetry Vol. 4, No. 6, pp. 1233-1236, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
Pergamon Press Ltd

THE PRODUCT OF BAKER'S YEAST REDUCTION OF ETHYL 2-CHLORO-3-OXOBUTANOATE AS A PRECURSOR OF THE 1-ETHOXYCARBONYL 2(S)-HYDROXYPROPYL RADICAL

Mourad Hamdani, Bernard De Jeso*, Hervé Deleuze, Annie Saux and Bernard Maillard*

Laboratoire de Chimie Organique, Associé au CNRS URA 35, Université Bordeaux 1,
351 Cours de la Libération, F-33405 TALENCE-CEDEX, France.

(*Received* 26 *November* 1992; *accepted* 4 *January* 1993)

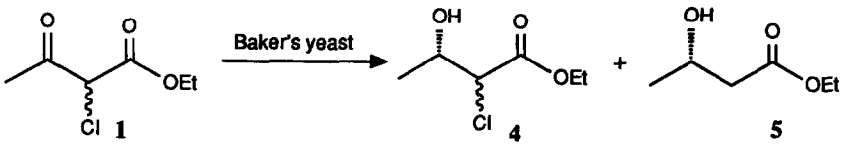
Abstract : Baker's yeast treatment of ethyl 2-chloro-3-oxobutanoate **1**, diethyl 2-acetylmalonate **2** and ethyl 2-cyano-3-oxobutanoate **3** was effected in order to obtain enantiomerically enriched compounds. In contrast to the reaction of **2** and **3**, efficient diastereo- and enantioselective reduction of **1** provided ethyl 2(R)-chloro-3(S)-hydroxybutanoate. This product was used as precursor of the 1-ethoxycarbonyl-2(S)-hydroxypropyl radical and the diastereoselectivity of the addition of this intermediate to alkenes was studied.

In the course of our studies on the preparation of homochiral compounds by free radical reactions (1,2), we decided to investigate the baker's yeast reduction of α-functionally substituted ethyl 3-oxobutanoates along with some free radical reactions of the resultant products. Ethyl 2-chloro-3-oxobutanoate **1**, diethyl 2-acetylmalonate **2** and ethyl 2-cyano-3-oxobutanoate **3** were chosen in order to use their reduction products as precursors of chiral free radicals.

Reduction of ethyl α-functionally substituted 3-oxobutanoates

According to the literature, only **1** had been submitted to baker's yeast reduction, AKITA and coworkers (3) obtaining equimolar amounts of both diastereoisomers.

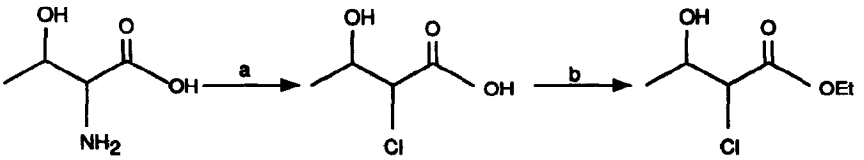
Compounds **1**, **2** and **3** were treated with baker's yeast in the conditions described in (1). Compound **1** yielded a mixture of the expected chlorohydroxyester **4** and ethyl 3(S)-hydroxybutanoate **5** in a ratio of 60/40 :



The production of **5**, with an optical purity of 96%, could be explained by the combination of a reductive dehalogenation of **1** followed by an oxo reduction since it is well known that ethyl 3-oxobutanoate is efficiently reduced by baker's yeast (1). Dehalogenation of **4** to give **5** was considered unlikely since **4** was unaffected under the conditions of reduction by baker's yeast. However, in order to define the exact origin of

5 an accurate study would need to be performed.

A comparison of 4 with the product of reduction of 1 by sodium borohydride according to (4) indicated a very high diastereoselectivity for the reaction (d.e. = 96%). The synthesis of enantiomers (2R, 3S) and (2S, 3R) of ethyl 2-chloro 3-hydroxybutanoate 4 from D and L threonine (5) allowed the identification of the product of reduction of 1 by baker's yeast as the enantiomer (2R, 3S) (table 1) :



a) $NaNO_2$, HCl 6N ; b) $NaHCO_3$, EtI, DMF

Origin	4 (configuration)	Yield (%)	d.e. (%)	e.e[a] (%)	$[\alpha]_D^{25}$ (c= 1, $CHCl_3$)
1	(2R, 3S)	40	96	96	+12,4
D- Threonine	(2R, 3S)	50	>98	>96	+12,4
L- Threonine	(2S, 3R)	50	>98	>96	-12,4

[a] Determined by gc after derivatization with (S)- α-methylbenzyl isocyanate

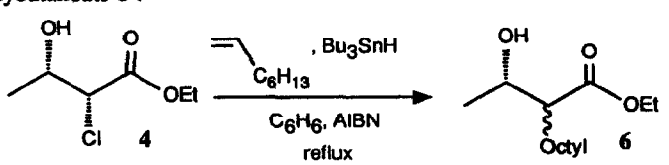
TABLE 1

Fermentation of compound 2 gave diethyl (1-hydroxyethyl)malonate in low yield (15%), the major part of 2 being deacetylated. No improvement in the yield could be obtained through changes in the experimental conditions (pH, reaction time, concentration of the various reactants).

Treatment of 3 with baker's yeast under the usual conditions (1) did not give the expected product : the only product recovered was a solid compound whose low solubility in organic solvents precluded satisfactory analysis.

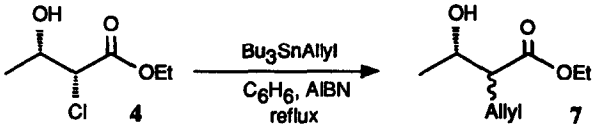
Ethyl 2(R)-chloro 3(S)-hydroxybutanoate as a precursor of 1-ethoxycarbonyl 2(S)-hydroxypropyl radical

The efficient abstraction of a chlorine atom by tributyltin radical (6) prompted us to use compound 4 as a source of the 1-ethoxycarbonyl 2(S)-hydroxypropyl radical. Indeed, the addition of this radical to alkenes could be a useful route to ethyl 2-alkyl-3(S)-hydroxybutanoate which may compensate for the inefficiency of the baker's yeast reduction of ethyl 2-alkyl-3-oxobutanoates that contain long n-alkyl groups (2). Treatment of 4 in the presence of oct-1-ene in large excess by tributyltinhydride (slow addition) provided ethyl 2-octyl-3-hydroxybutanoate 6 :



Comparison, by gas chromatography, of this mixture with a sample of ethyl 3(S)-hydroxy-2(S)-octylbutanoate, prepared by the stereoselective alkylation of 3(S)-hydroxybutanoate according to a method developed by FRATER (7), indicated that the major isomer was (2R, 3S) (Table 2).

The similar free radical reaction between allyltributyltin and **4** produced ethyl 2-allyl 3-hydroxybutanoate **7** :



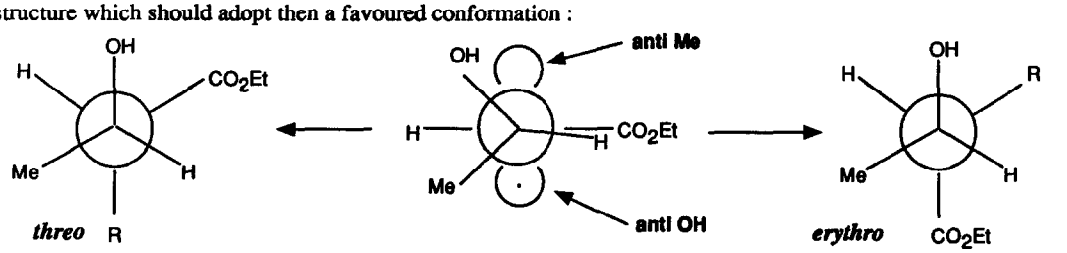
Comparison with a sample of the isomer (2R, 3S) obtained previously (2) indicated that the major isomer was (2S, 3S) (Table 2). These results agree with a study of HART (8) on the reaction of allyltin with an achiral seleno free radical precursor.

Product	Origin	Configuration	Yield (%)	d.e. (%)	e.e[a] (%)
6	Addition	(2R, 3S)	51	36	95
	Alkylation (7)	(2S, 3S)	85	96	95
7	Addition	(2S, 3S)	55	10	95
	Reduction (1)	(2S, 3S)	75	56	97

[a] Determined by gc after derivatization with (S)- α-methylbenzyl isocyanate

TABLE 2

GIESE (9) has shown that a radical containing an ester function and a stereogenic carbon has a favoured conformation determined by allylic strain (10). The radical produced from **4** presents such a structure which should adopt then a favoured conformation :

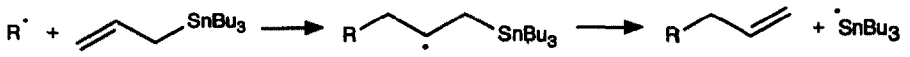


Methyl or hydroxy substituents should then orientate the reaction : attack anti to the hydroxyl group would lead to the threo isomer and anti to the methyl group the erythro. Taking into account the small steric difference between these two substituents, it is not surprising that we found very low diastereoselectivity in these reactions.

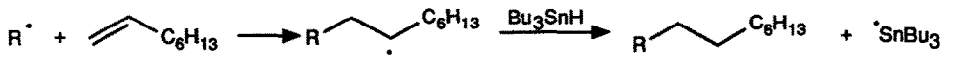
Allyl transfer proceeded preferentially anti to the hydroxyl group while the addition to octene occured anti to the methyl. These results were in total contrast to those of GIESE (11) where addition of

t-Bu-CHMe-CH(OAc)· to either allyltributyltin, ethyl acrylate or acrylonitrile gave similar diastereoselectivities.

The generally accepted mechanism for the allylation reaction is a two step process (12) :



with a first step similar to the addition to oct-1-ene :



Assuming similar transition states for them, one would attribute the inversion of selectivity to steric interactions, the bulkiness of tri-n-butyltinmethyl moiety being different from that of the hexyl group. Nevertheless, taking into account the angle of attack onto the double bond (13), such an apparent effect of the size of the group on the carbon α to the double bond is surprising. Another explanation could be the existence of two different mechanisms for both reactions of addition as questioned by previous authors (14).

In conclusion, baker's yeast reduction of ethyl 2-chloro-3-oxobutanoate readily provides ethyl 2(R)-chloro 3(S)-hydroxybutanoate which acts as a precursor for the addition of the ethyl 1-ethoxycarbonyl 2(S)-hydroxypropyl radical to unsaturated compounds.

Literature

(1) Hamdani M., De Jeso B., Deleuze H. and Maillard B., *Tetrahedron Asymmetry*, **2**, 1991, 867.

(2) Previous paper in this issue.

(3) Akita H., Matsukura H., Oishi T., *Tetrahedron Lett.*, 1986, **27**, 5397.

(4) Santaniello E., Ponti F., Manzocchi A., *Synthesis*, 1978, 891.

(5) Hintzer K. Koppenhoefer B;, Schurig V., *J. Org. Chem.*, 1982, **47**, 3850.
Amouroux R., Gerin B., Chastrette M., *Tetrahedron*, 1985, **41**, 5324.

(6) Pereyre M., Quintard J-P., Rahm A., *Tin in Organic Synthesis*, Butterworths,London, 1987, p.35 and references.

(7) Frater G., Muller U., Gunther W., *Tetrahedron*, 1984, **40**, 1269.

(8) Hart D.J. and Krishnamurthy R., *J. Org. Chem.*, 1992, **57**, 4457.

(9) Giese B., Damm W., Wetterich F., Zeitz H.G., *Tetrahedron Lett.*, 1992, **33**, 1863.

(10) Giese B., Bulliard M., Zeitz H.G., *Synlett.*, 1991, 425.

(11) Giese B., Damm W., Dickhaut J., Wetterich F., *Tetrahedron Lett.*, 1991, **32**, 6097.

(12) Grignon J., Pereyre M., Servens C., *J. Organometal. Chem.*, 1975, **96**, 225.
Migita T., Nagai K., Kosugi M., *Bull. Chem. Soc. Jpn.*, 1983, **56**, 2480.
Russel G.A., Ngoviwatchai P., Tashtouch H.I., *Organometallics*, 1988, **7**, 696.

(13) Easton C., *Sci. Prog. Oxf.*, 1983, **68**, 503.

(14) Curran D.P., van Elburg P.A., Giese B., Gilges S., *Tetrahedron Lett.*, 1990, **31**, 2861.