Tetrahedron Letters,Vol.28,No.13,pp 1447-1450,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

A FACILE SYNTHESIS OF OPTICALLY PURE L-ARMENTOMYCIN AND ITS D-ISOMER. HIGHLY ENANTIOSELECTIVE REDUCTION OF THE C—C DOUBLE BOND OF METHYL (*E*)- AND (*Z*)-2,4,4-TRICHLORO-2-BUTENOATE BY USING BAKER'S YEAST

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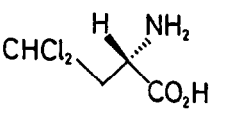
Abstract: Optically pure L-armentomycin [(*S*)-2-amino-4,4-dichlorobutanoic acid] and its D-isomer [(*R*)-2-amino-4,4-dichlorobutanoic acid] were prepared by using methyl (*E*)- and (*Z*)-2,4,4-trichloro-2-butenoate as key intermediate, which were reduced with baker's yeast to (*R*)- and (*S*)-2,4,4-trichlorobutanoate in 84~92 and 97~98% ee, respectively, in 60~65% yields.

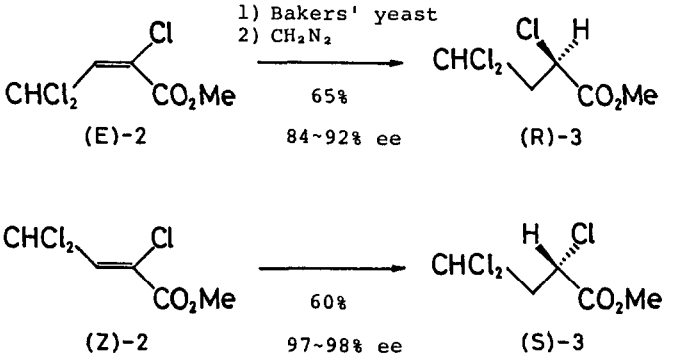
L-Armentomycin [(*S*)-2-amino-4,4-dichlorobutanoic acid] [(*S*)-**1**][1] known as a naturally occurring antibiotic agent is typical of a series of halogeno α-amino acids which possess interesting biological activities.[2] Since it was isolated from the culture broth of *Streptomyces armentosus* var. *armentosus* in 1967,[1a] two synthetic works have been reported: one is an electrochemical synthesis of L-armentomycin starting from L-methionine[2d] and the other a synthesis of the racemate from acrylic acid and chloroform.[2f]

We now report a microbial asymmetric synthesis of both L- and D-armentomycin (**1**) starting from dichloroacetaldehyde and methyl α-chloroacetoacetate, in which a highly enantioselective yeast-reduction of the C—C double bond of methyl (*E*)- and (*Z*)-2,4,4-trichloro-2-butenoate (**2**) is involved as the key reaction. The remarkable feature of this reduction is the highly effective stereochemical control for each geometrical isomer **2** to produce (*R*)- or (*S*)-α-chloro ester **3**. Thus, (*E*)-**2** afforded (*R*)-**3** in 84~92% ee while (*Z*)-**2** afforded (*S*)-**3** in 97~98% ee. Such a stereochemical control by using baker's yeast is unprecedented, although α,β-unsaturated carbonyl compounds have been reported to undergo microbial reduction at the C—C double bond.[3,4]



(S)-1

Methyl (*E*)-2,4,4-trichloro-2-butenoate [(*E*)-**2**][5] (328 mg, 1.61 mmol) was added to a culture solution[6] (400 mL) of immobilized baker's yeast (containing 4 g of dry yeast)[7] and the mixture was stirred for 30 h at 32°C. The mixture was filtered and the filtrate was extracted with ethyl acetate after being adjusted to pH 2 with aq HCl. The extract was dried ($MgSO_4$) and evaporated to give the hydrolyzed product of (*R*)-**3**, which was esterified with CH_2N_2. Then the crude ester was passed through a silica gel column (hexane—ether, 20:1) to



afford (*R*)-3 (216 mg) in 65% yield: $[\alpha]_D^{25}$ +42.4° (c 1.32, $CHCl_3$). In a similar way, (*Z*)-2 was reduced to (*S*)-3 in 60% yield: $[\alpha]_D^{25}$ -44.0° (c 1.69, $CHCl_3$). The IR and ^1H NMR data were in agreement with those reported for the racemate.[8] The optical purity was determined to be 92% ee for the former and 98% ee for the latter by using ^1H NMR signal intensity of the methyl group in the presence of Eu(hfc)$_3$ (Figure 1).[9] The absolute configuration was determined to be *R* and *S*, repectively, after conversion to 1.

It should be noted that the reduction product was obtained as the hydrolyzed acid of 3. The hydrolysis is likely catalyzed by hydrolytic enzymes involved in yeast cells.[10] We found that, when ethyl (*Z*)-2,4,4-trichlorobutenoate was used as substrate, 62% of the ester was recovered intact under the conditions used, being accompanied by a trace amount of the reduction product as hydrolyzed acid. Therefore, it is quite probable that the substrate 2 was reduced after hydrolysis.

There remains an important question why (*E*)-2 was reduced to (*R*)-3 with an ee value somewhat lower than that for (*Z*)-2 to (*S*)-3. This may arise from the isomerization of the *E* isomer to the *Z* isomer and/or from the lower enantio-

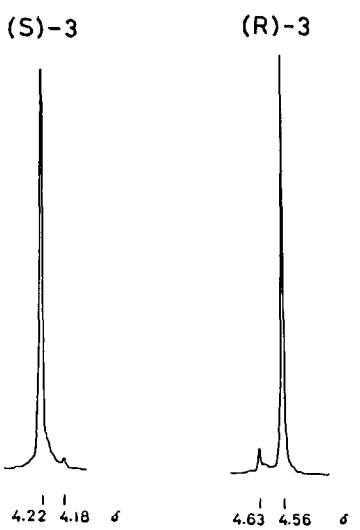
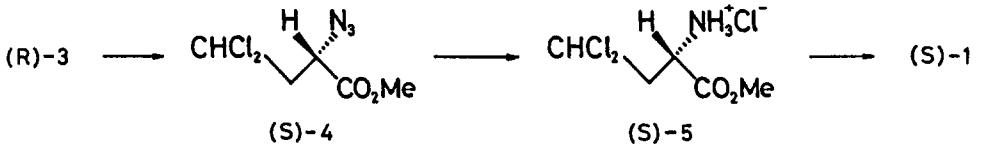


Figure 1. The ^1H NMR signals of the methyl group of (*R*)- and (*S*)-3 in the presence of 160 mol% Eu(hfc)$_3$ in CCl_4–$CDCl_3$ (3:1) at 50°C (100 MHz).



selectivity of the yeast reductase toward the *E* isomer. We found that both the *E* and *Z* isomers are stable and can be stored without isomerization, and that the *E* isomer is not isomerized to the *Z* isomer in the culture solution. Therefore, it is concluded that the ee values reflect the enantioselectivity of the yeast reductase.

The use of immobilized yeast in calcium alginate gel beads enabled the separation of product from the yeast cells very easy. Favorably, no product was extracted from the gel beads, indicating that all of the product diffused throughout the yeast cell and the gel compartment.

The conversion of 3 to 1 via 4[11] and 5[12] was carried out according to the method reported for the racemate,[2f] to afford crude (*S*)-1 from (*R*)-3 in 54% yield,[13] $[\alpha]_D^{25}$ +17.6° (c 0.66, aq HCl, pH 1.0) and crude (*R*)-1 from (*S*)-3 in 51% yield, $[\alpha]_D^{25}$ -22.7° (c 0.75, $CHCl_3$) [lit.[1a] $[\alpha]_D^{25}$ +26.2° (c 0.75, aq HCl, pH 1.0) for L-armentomycin]. These were recrystallized once from methanol–water (18:1) to give colorless crystals of (*S*)-1 in 53% yield, $[\alpha]_D^{25}$ +26.8° (c 0.71, aq HCl, pH 1.0) and (*R*)-1 in 63% yield, $[\alpha]_D^{25}$ -26.7° (c 0.72, aq HCl, pH 1.0), both in 100% optical purity.

Acknowlegment. This work was supported by a Grant-in-Aid (No. 60110001) from the Ministsy of Education, Science and Culture of Japan.

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