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Highly stereoselective bioreduction and one-way isomerization of 2-alkyl-4,4,4-trichloro-2-butenals

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Abstract—This article describes a highly stereoselective bioreduction of 2-alkyl-4,4,4-trichloro-2-butenals (**1a**: Me, **1b**: Et) mediated by baker's yeast (*Saccharomyces cerevisiae*). The *E*-isomers were regiospecifically converted into the saturated alcohols **2** with high enantioselectivity, whereas the *Z*-isomers generated in situ by a competitive one-way isomerization were reduced only into the corresponding allyl alcohols **3** during the reactions.

The baker's yeast mediated bioreduction of disubstituted acroleins is an efficient way for preparing chiral primary alcohols, although introduction of 3-aryl groups seems to be important in most cases.[1] Recently, we found that the bioreduction of 2-ethylhex-2-enal, a substrate without an 3-aryl group, proceeded smoothly, giving high yield of (*S*)-2-ethylhexan-1-ol in high enantioselectivity.[2] This discovery aroused our interest to further investigate the bioreduction of other aliphatic acroleins.

Butyrolactones deserve great interest in synthetic and natural products chemistry.[3] Several chemical synthetic methods for β-alkyl γ-butyrolactones have been developed and reported during the last years.[4] Besides the chemical methods, two chemo-enzymatic synthetic routes were also reported about two decades ago,[5] in which 2-methyl-3-(2-furyl)acrolein and ethyl 4,4-dimethoxy-3-methylcrotonate were used as the starting materials. The apparent disadvantages for the former case lie in the subsequent oxidation of the furan ring, and for the latter case in the low yield of bioreduction product. Considering that trichloromethyl is a good potential carboxylic group, we think that optically pure 2-alkyl-4,4,4-trichloro-2-butanol should be a good precursor for 3-alkylbutyrolactone. Therefore, we have recently investigated the bioreduction of 2-alkyl-4,4,4-trichloro-2-butenals mediated by the baker's yeast for this purpose. In our experiments, two interesting phenomena have been observed. One is the unexpected spontaneous one-way isomerization of the *E*-isomer to the *Z*-isomer of 2-alkyl-4,4,4-trichloro-2-butenals. Another is the regiospecific bioreduction of the two isomers mediated by baker's yeast.

Substrates **1a** and **1b** were prepared by cross-aldol reaction of chloral with propanal or butanal and subsequent dehydration of the aldol products catalyzed by toluenesulfonic acid in toluene (Scheme 1),[6] and characterized by NMR spectroscopy and IR spectrum.[7] The biocatalyst utilized in this work was the Angel instant dry yeast.

A typical bioreduction was performed by stirring a mixture of 500 mg of substrate **1a** and 17.0 g of dry baker's yeast in 210 mL of distilled water at 30 °C. The main products were saturated alcohol **2a**[8] and an allyl alcohol **3a** as characterized by ^{1}H NMR and IR. We attempted to identify the structure of the allyl alcohol by preparing **4a**[9] through the reduction of substrate **1a** with $NaBH_4$. The ^{1}H NMR spectrum of compound **4a**, however, was different from that of product **3a**. Actually, the chemical shift of olefinic proton of product **3a** was 6.10, whereas that of **4a** was 5.93. In view of the similarity of their ^{1}H NMR spectra, allyl alcohol **3a** was assigned to be (*Z*)-2-methyl-4,4,4-trichlorobuten-2-ol,[9] a geometric isomer of **4a**. In fact, only *Z*-isomer **3a** rather than the expected *E*-isomer **4a** was generated during the reaction (Scheme 2).

Keywords: Bioreduction; Baker's yeast; One-way isomerization; 4,4,4-Trichloro-2-butenal.
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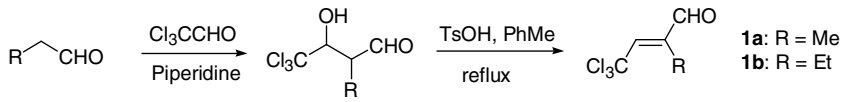
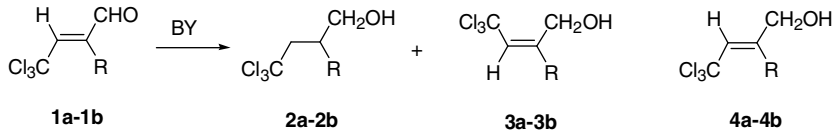


Scheme 1.



Scheme 2.

Further evidence to support the structure assignment came from GC analysis. From their structural feature, the polarity of *Z*-isomer **3a** was estimated to be higher than that of *E*-isomer **4a**, and the magnitude of their polarity was correlated with the retention time in GC. Actually, the accurate retention times of **3a** and **4a** were 18.33 and 10.97 min, respectively. GC conditions: the column AE-PEG-20 M 30 m × 0.25 mm, the carrier gas N_2, the column temperature 80–180 °C, 3 °C/min. In addition, the ee value of **2a** was determined by gas chromatography with chirasil-dex CB 25 × 0.25 mm column (DIKMA) under the GC conditions: the carrier gas N_2, the column temperature 90–180 °C, 2 °C/min. The retention times for the enantiomers of **2a** were 33.12 (minor) and 33.40 (main), respectively. The ee value of **2a** determined is given in Table 1.

As shown in Table 1, the bioreduction reaction of **1a** proceeded quickly at 30 °C and was completed within 2 h. The molar ratio of the saturated alcohol **2a** and the allyl alcohol **3a** was 65:35 at 0.5 h (entry 1), and gradually decreased to 43:57 at 8.0 h (entry 6). The formation of *Z*-isomer **3a** clearly indicated that a competitive *E*→*Z* isomerization of **1a** occurred during the bioreduction, though *Z*-isomer of **1a** was not detected by GC during the reaction. During the course of the reaction, the molar ratio of **2a**–**3a** was almost kept constant, revealing that further bioreduction of **3a** into **2a** would be very difficult. The reaction behavior for *E*-isomer **4a** was also assessed by shaking a mixture of **4a** (60 mg) and the baker's yeast (2.0 g) in water at 30 °C for 24 h. As a result, no detectable reduction product **2a** was obtained. This experiment confirmed that the existence of electron-withdrawing trichloromethyl group would make the bioreduction of allyl alcohol to its corresponding saturated alcohol difficult.

Previously we reported that the α-alkyl group has a marked effect on the bioreduction of substituted acroleins.[2] For this reason, the bioreduction of **1b** with an α-ethyl group was studied next. The experiment was performed according to the same procedures described above. The main products afforded in the reaction were the saturated alcohol **2b**[10] and the allyl alcohol **3b**.[11] The ee value of **2b** determined by chiral GC was about 99%. All the results are given in Table 2. It was clear that the reduction rate of **1b** was somewhat slower than that of **1a** under the same conditions. In addition, the molar ratio of the saturated alcohol **2b** to the allyl alcohol **3b** was apparently higher than that of **2a**–**3a**. Moreover, there was no distinct change in the molar ratio of **2b**–**3b** during the reaction after **1b** was completely consumed, indicating that a continuous reduction of **3b** into **2b** was quite difficult under the reaction conditions. Similarly, the reduction reactivity of the allyl alcohol **4b**,[11] a geometric isomer of **3b**, also proved to be very low for no detectable **2b** was formed in the subsequent reduction by baker's yeast in water.

According to these experimental observations, we could suggest that the reaction of substrate **1** (*E*-isomer) proceeded smoothly along with the bioreduction of C=C bond and a competitive *E*→*Z* isomerization. The *Z*-isomer generated in situ during the reaction, however, preferred to react via bioreduction of the C=O bond, giving only *Z*-allyl alcohol **3**. Moreover, the molar ratio of **2**–**3** was greatly dependent upon the relative rate of simultaneous reduction and isomerization. The reason for the favorable formation of **2b** might be explained by the relatively slow isomerization of **1b** in water. These processes are illustrated in Scheme 3.

The reaction medium was examined next owing to the marked effect of reaction medium on yeast mediated bioreduction. As a consequence, compounds **2** and **3** were still afforded as the main products, but their molar ratio changed markedly depending upon the reaction medium. When the reaction of **1a** was carried out in a

Table 1. The bioreduction of **1a** in water at 30 °C[a]

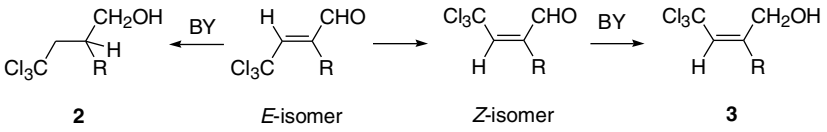
Entry	Time (h)	Conversion (%)	**2a/3a**	ee
1	0.5	54	65:35	94.5
2	1.0	86	57:43	—
3	2.0	>99	46:54	—
4	4.0	>99	44:56	—
5	8.0	>99	43:57	—
6	24.0	>99	45:55	95.5

[a] All the data determined by GC.

Table 2. The bioreduction of **1b** in water at 30 °C[a]

Entry	Time (h)	Conversion (%)	**2b/3b**	ee
1	0.5	23	99:1	98.5
2	1.0	49	86:14	—
3	2.0	68	81:19	—
4	4.0	99	78:22	—
5	8.0	>99	79:21	—
6	24.0	>99	78:21	99.0

[a] All the data determined by GC.



Scheme 3.

potassium phosphate buffer (PBS, 0.1 M, pH 7.5), the yield of **2a** decreased to 11% in comparison with the situation in water, and allyl alcohol **3a** became the major product instead (Table 3, entry 2). A sharp decline in the yield of **2a** was observed when substrate **1a** was first shaken in this buffer for 1 h before adding baker's yeast (entry 3). A similar decrease in the yield of **2a** also occurred when substrate **1a** was emulsified using a certain amount of surfactant Tween 80 (entry 4). In the case of **1b**, a marked decrease in the yield of **2b** was also observed in these media (entries 6–9). In contrast, the formation of **2a** was favored to some extent when water–petroleum ether biphasic system was used as the reaction medium (entry 5). The striking effect of reaction media on the product distribution might be attributed to the change in relative rate of simultaneous bioreduction and isomerization of **1a** and **1b**.

In order to find out the driving force for initiating the $E \rightarrow Z$ isomerization, we have checked the chemical behavior of substrates **1a**,**b** in the aqueous medium. When a mixture of **1** (30 mg) and water or PBS (12 mL) was shaken at 30 °C for a certain period, the *Z*-isomer formed gradually. The structure of *Z*-isomer was characterized by converting it into the allyl alcohol **4** via reduction with $NaBH_4$. The conversion of *E*-isomer **1** was determined by GC analysis, and all the results are given in Table 4. Surprisingly, it was found that the *E* isomer could be converted completely into the *Z* isomer for each of **1a** and **1b**, that is, a spontaneous one-way $E \rightarrow Z$ isomerization did occur in aqueous phase. In addition, we noticed that the one-way $E \rightarrow Z$ isomerization for **1a** proceeded more rapidly than that for **1b**, and that in potassium phosphate buffer was more quickly than in water.

Table 3. Effect of the medium on the reaction[a]

Entry	Media	Substrate	**2** (Yield %)
1	H_2O	**1a**	**2a** (45)
2	PBS	**1a**	**2a** (11)
3	PBS[b]	**1a**	**2a** (<1)
4	H_2O/Tween 80	**1a**	**2a** (12)
5	H_2O/petroleum	**1a**	**2a** (53)
6	H_2O	**1b**	**2b** (78)
7	PBS	**1b**	**2b** (45)
8	PBS[b]	**1b**	**2b** (19)
9	H_2O/Tween 80	**1b**	**2b** (20)

[a] Compound **1** (60 mg), BY (2.0 g), solvent (20 mL), Tween 80 (0.60 g), petroleum ether (20 mL), at 30 °C for 8 h.
[b] Compound **1** was first shaken for 1 h in PBS, then BY added.

Table 4. Isomerization of acroleins **1a**,**b**

Entry	Substrate	Media	Time (min)	Conversion (%)
1	**1a**	PBS	10	46
2	**1a**	PBS	20	100
3	**1a**	H_2O	10	36
4	**1a**	H_2O	20	75
5	**1a**	H_2O	40	100
6	**1b**	PBS	10	15
7	**1b**	PBS	20	45
8	**1b**	PBS	40	74
9	**1b**	PBS	120	100
10	**1b**	H_2O	10	4
11	**1b**	H_2O	20	15
12	**1b**	H_2O	40	48
13	**1b**	H_2O	60	71
14	**1b**	H_2O	120	100

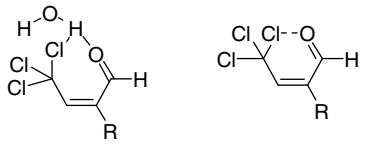


Figure 1.

To our best knowledge, it was the first case that the substituted acroleins reacted via spontaneous one-way $E \rightarrow Z$ isomerization in aqueous phase hitherto, despite the fact that an equilibrium isomerization for ethyl 4-oxo-3-methylcrotonate was reported about two decades ago.[12] From the extremely favorable formation of *Z*-isomer, we can believe that there was a specially strong interaction between formyl and trichloromethyl groups. A plausible explanation for this special interaction might be drawn by supposing the formation of hydrogen-bonding (a) or halogen-bonding (b) between them as depicted in Figure 1. Presently, the possibility of forming halogen-bonding is rather high because of the favorable six-membered ring system.

In summary, we consider that the bioreduction of 2-alkyl-4,4,4-trichloro-2-butenals by baker's yeast is a valuable reaction for preparing chiral primary alcohol. A regiospecific bioreduction of C=C and C=O bonds is indeed observed in this work. The introduction of trichloromethyl group to C=C bond of the acroleins leads to the occurrence of one-way isomerization and the extremely low reactivity of the corresponding allyl alcohol toward baker's yeast. This work implies that substituents at the α- or β-sites have a marked effect on its bioreduction rate and product distribution, and the details are subject to further investigation.

Acknowledgment

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6. Spectroscopic data for **1a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.45 (s, 1H), 7.06 (s, 1H), 2.13 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.16, 152.20, 142.79, 90.96, 10.42. IR ν (cm^{-1}): 3062, 2837, 2723, 1702, 1645. For **1b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.40 (s, 1H), 7.00 (s, 1H), 2.68 (q, $J = 7.6$ Hz, 2H), 1.12 (t, $J = 7.6$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.33, 151.74, 147.75, 90.88, 18.22, 12.12. IR ν (cm^{-1}): 3058, 2834, 2723, 1699, 1634.
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8. Spectroscopic data for **2a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.66 (dd, $J_1 = 10.6$ Hz, $J_2 = 5.8$ Hz, 1H), 3.59 (dd, $J_1 = 10.6$ Hz, $J_2 = 5.8$ Hz, 1H), 2.98 (dd, $J_1 = 14.0$ Hz, $J_2 = 3.8$ Hz, 1H), 2.56 (dd, $J_1 = 14.0$ Hz, $J_2 = 3.8$ Hz, 1H), 1.61–1.65 (m, 1H), 1.19 (d, $J = 6.8$ Hz, 3H).
9. Spectroscopic data for **3a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.10 (s, 1H), 3.72 (d, $J = 11.2$ Hz, 1H), 3.53 (d, $J = 11.2$ Hz, 1H), 1.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.37, 121.92, 73.66, 69.04, 23.06. For **4a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.93 (s, 1H), 3.73 (d, $J = 11.2$ Hz, 1H), 3.55 (d, $J = 11.2$ Hz, 1H), 1.44 (s, 3H).
10. Spectroscopic data for **2b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.79 (dd, $J_1 = 15.2$ Hz, $J_2 = 4.8$ Hz, 1H), 3.69 (dd, $J_1 = 15.2$ Hz, $J_2 = 4.8$ Hz, 1H), 2.92 (dd, $J_1 = 14.4$ Hz, $J_2 = 4.8$ Hz, 1H), 2.62 (dd, $J_1 = 14.4$ Hz, $J_2 = 4.8$ Hz, 1H), 1.71–1.74 (m, 1H), 1.61–1.65 (m, 2H), 1.03 (t, $J = 7.2$ Hz, 3H).
11. Spectroscopic data for **3b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.98 (s, 1H), 3.75 (d, $J = 11.2$ Hz, 1H), 3.55 (d, $J = 11.2$ Hz, 1H), 1.75 (q, $J = 7.6$ Hz, 2H), 0.95 (q, $J = 7.6$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.27, 121.59, 76.76, 67.69, 29.45, 7.78. For **4b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.82 (s, 1H), 3.77 (d, $J = 11.6$ Hz, 1H), 3.66 (d, $J = 11.6$ Hz, 1H), 1.82 (q, $J = 7.6$ Hz, 2H), 0.91 (q, $J = 7.6$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 129.44, 122.76, 80.95, 63.34, 25.67, 7.80.
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