The Baker's Yeast Reduction of the β-Keto Aldehydes in the Presence of a Sulfur Compound

Ryuuichirou Hayakawa, Makoto Shimizu*

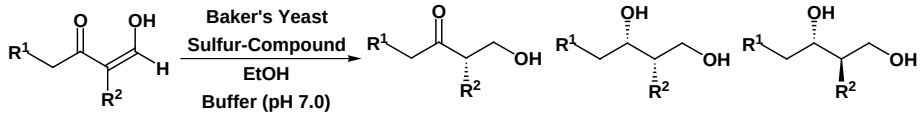
Department of Chemistry for Materials, Mie University, Tsu, Mie 514-8507, Japan

Received 19 May 1999

Abstract: Improved enantio- and diastereoselectivity was achieved in the baker's yeast reduction of β-keto aldehyde derivatives using a sulfur compound as an additive. The resulting enantiomerically pure diol was transformed into serricornin, a sex pheromone of the cigarette beetle.

Key words: α-substituted-β-keto aldehyde, baker's yeast, sulfur compound, chiral 1,3-diol, serricornin

The baker's yeast reduction of a carbonyl compound is one of the most useful methods for the preparation of the optically active alcohols.[1] Especially the baker's yeast reduction of β-keto esters has been widely investigated because of its synthetic utility. However, there have been numerous examples that afforded unsatisfactory results, low chemical yield, and/or low selectivity, mainly because of the participation of multiple enzymes with different enantioselectivity.[1] A number of methods have been reported for the improvement of the enantioselectivity of the baker's yeast reduction of β-keto ester derivatives, involving some modification of the substrate,[2] addition of an additive as a selective inhibitor of reductase,[3] addition of an inorganic salt,[4] immobilization of baker's yeast,[5] thermal treatment of yeast cells,[6] or use of an organic solvent .[7] However, the rate of reduction and chemical yield usually decreased in such cases. We have found that the reactivity and enantioselectivity of the baker's yeast reduction could be improved using a sulfur compound as an additive.[8] We are interested in the generality of this method. On the other hand, the baker's yeast reduction of α-substituted β-keto aldehydes has not been reported although the resulting chiral 2-substituted-1,3-diol derivatives are useful intermediates. Now we wish to report an efficient method of the bakers' yeast reduction of α-substituted β-keto aldehyde derivatives using a sulfur compound. The β-keto aldehydes as substrates were prepared from the corresponding ketones by formylation.[9] The β-keto aldehydes as substrates were prepared from the corresponding ketones by formylation.[9] In a typical procedure of the baker's yeast reduction, a suspension of 3.1 g of dry baker's yeast (S. I. Lesaffre) in 21 mL of phosphate buffer (pH 7.0) was stirred for 0.5 h at ambient temperature. To the resulting suspension a sulfur compound was added. After 0.5 h stirring, 2.1 mL of an ethanol solution of 3-formyltetrahydrothiopyran-4-one **1b** (100 mg, 0.69 mmol) was added to the suspension of bakers' yeast. After 24 h stirring, Celite and ethyl acetate were added to the reaction mixture, and the whole mixture was stirred for 0.5 h. The resulting mixture was filtered through a Celite pad. The filtrate was extracted with ethyl acetate (5 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography. The results are summarized in Table 1.



1a ; R_1 = Me, R_2 = Me
1b ; R_1, R_2 = CH_2SCH_2

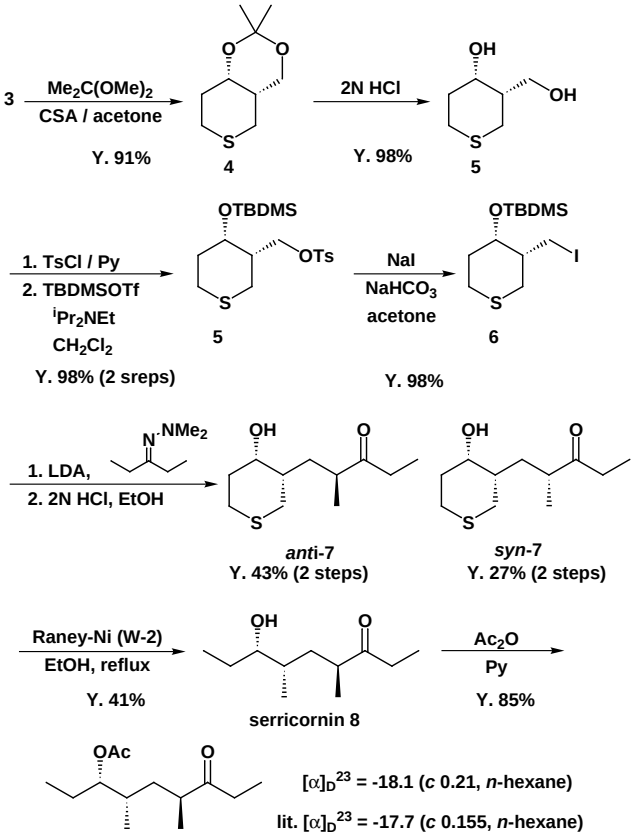
Table 1 The Baker's Yeast Reduction of β-Keto Aldehyde Derivatives

Entry	Substrate	Sulfur-Compound (equiv.)	yield (%)[a]	**2** :	*syn*-**3** :	*anti*-**3** [c] (% ee)
1	**1a**	none	65	100 (36)[b] :	0 :	0
2	**1a**	$HSCH_2CH_2NH_2$•HCl (1.0)	31	100 (67)[b] :	0 :	0
3	**1a**	L-Cysteine (3.0)	47	100 (73)[b] :	0 :	0
4	**1b**	none	67	0 :	82 (84) :	18 (>99)[d]
5	**1b**	Me_2S (2.0)	81	0 :	80 (90) :	20 (>99)[d]
6	**1b**	L-Cysteine (3.0)	26	0 :	90 (95) :	10 (>99)[d]
7	**1b**	L-Methionine (5.0)	50	0 :	78 (93) :	22 (97)[d]
8	**1b**	DMSO (3.0)	82	0 :	88 (>99) :	12 (>99)[d]

[a] Isolated yield. [b] Determined by GC (Chiraldex G-TA) analysis. [c] Determined by 500 MHz ^{1}H NMR analysis of the crude product of the corresponding acetonide derivative **4**. [d] Determined by HPLC (Daicel Chiralcel OD) analysis of the corresponding dibenzoate derivative.

The baker's yeast reduction of 2-methyl-3-oxopentanal **1a** gave (*S*)-2-methyl-3-oxopentanol **2a** with 36% ee. The absolute stereochemistry was determined by its derivatization to the dibenzoate derivative of the corresponding diol derivative, and comparison of the retention time of HPLC (Daicel chiralcel OD) with the known dibenzoate derived from diol **3**. Improved enantioselectivity was obtained using a sulfur compound with up to 73% ee. The use of L-cysteine as an additive was the most effective in the reduction of 2-methyl-3-oxopentanal **1a**, although the result was not completely satisfactory. Therefore the baker's yeast reduction of 3-formyltetrahydrothiopyran-4-one **1b** was next investigated, because it has been known that introduction of a sulfur atom to the substrate improves the enantioselectivity and the sulfur can be removed via either a reductive or oxidative process.[10] The corresponding diol derivative **3** was obtained in the baker's yeast reduction of 3-formyltetrahydrothiopyran-4-one **1b**, while the reduction of 2-methyl-3-oxopentanal **1a** gave the corresponding 3-oxoalkanol derivative **2**. The difference in the reactivity may be due to the bulkiness of the substrate. A similar example has been reported in the baker's yeast reduction of the β-keto ester derivatives. The reduction of 3-methoxycarbonyltetrahydrothiopyran-4-one gave the reduced product, while reduction of methyl 2-methyl-3-oxopentanoate did not proceed.[11] The *syn*-selectivity was improved using a sulfur compound such as L-cysteine or DMSO with a ratio of 90 : 10 or 88 : 12, respectively. The relative configuration was determined by 500 MHz ^{1}H NMR analysis of the crude product of the corresponding acetonide derivative **4**.[12] Improved enantioselectivity was also obtained using a sulfur compound. The best enantioselectivity of *syn*-**3a** was achieved using DMSO as an additive in up to >99% ee. The absolute stereochemistry was established by its derivatization to sericornin acetate, and comparison of the optical rotation.

The enantiomerically pure 1,3-diol derivative **3** was transformed into sericornin. Sericornin is a sex pheromone produced by the female cigarette beetle (*Lasioderma sericorne F*.), which is a serious pest of cured tobacco leaves.[13] The diastereomeric mixture of the diol derivative **3** was separated with flash chromatography after the transformation into the acetonide derivative **4**. Selective tosylation of the primary hydroxy group of the diastereo- and enantiomerically pure diol *syn*-**3**, followed by the protection of the secondary hydroxy group with TBDMS and iodination of the tosylate gave the iodide derivative **6** in high yield. Alkylation of the hydrazone with the iodide **6** followed by hydrolysis for construction of the skeleton of sericornin gave a separable diastereomeric mixture of the coupling product **7**. The *anti*-isomer of the alkylated product *anti*-**7** was reduced with Raney-nickel (W-2) to give sericornin **8**. The absolute stereochemistry was established by comparison of the optical rotation of sericornin acetate **9**.[13b]



In summary, improved enantio- and diastereoselectivity in the baker's yeast reduction of β-keto aldehyde derivatives was achieved using a sulfur compound as an additive. Previously, the baker's yeast reduction of β-keto aldehyde derivatives has not been reported. The homochiral diol was transformed into sericornin in enantiomerically pure form in short steps and high yield, demonstrating the synthetic usefulness of the use of a sulfur compound as an additive in the baker's yeast reduction.

References

(1) (a) Servi, S. *Synthesis* **1990**, 1. (b) Csuk, R.; Glänzer, B. I. *Chem. Rev*. **1991**, *91*, 49. (c) Jones, J. B. In *Comprehensive Organic Synthesis*; Trost B. M., Ed.; Pergamon Press: New York, 1991, *8*, p 183. (d) Santaniello, E.; Ferraboschi, P.; Grisenti, P. In *Encyclopedia of Reagents for Organic Synthesis*; Paquett, L. A., Ed.; John Wiley & Sons: Chichester, 1995; *1*, p 233.

(2) (a) Zhou, B.; Gopalan, A. S.; Middlesworth, F. V.; Shieh, W. -R.; Sih, C. J. *J. Am. Chem. Soc*. **1983**, *105*, 5925. (b) Fuganti, C.; Grasselli, P.; Casati, P.; Carmeno, M. *Tetrahedron Lett*. **1985**, *26*, 101.

(3) (a) Nakamura, K.; Inoue, K.; Ushio, K.; Oka, S.; Ohno, A. *Chem. Lett*. **1987**, 679. (b) Nakamura, K.; Kawai, Y.; Oka, S.; Ohno, A. *Bull. Chem. Soc. Jpn*. **1989**, *62*, 875. (c) Nakamura, K.; Kawai, Y.; Ohno, A. *Tetrahedron Lett*. **1990**, *31*, 267. (d) Ushio, K.; Hada, J.; Tanaka, Y.; Ebara, K. *Enzyme Microb. Technol*. **1993**, *15*. 222.

(4) Nakamura, K.; Kawai, Y.; Oka, S.; Ohno, A. *Tetrahedron Lett*. **1989**, *30*, 2245.
(5) (a) Nakamura, K.; Higaki, M.; Ushio, K.; Oka, S.; Ohno, A. *Tetrahedron Lett*. **1985**, *26*, 4213. (b) Naoshima, Y.; Hasegawa, H. *Chem. Lett*. **1987**, 2379.
(6) (a) Nakamura, K.; Kawai, Y.; Nakajima, N.; Ohno, A. *J. Org. Chem*. **1991**, *56*, 4778. (b) Nakamura, K.; Kawai, Y.; Ohno, A. *Tetrahedron Lett*. **1991**, *32*, 2927. (c) Kawai, Y.; Kondo, S.; Tsujimoto, M.; Nakamura, K.; Ohno, A. *Bull. Chem. Soc. Jpn*. **1994**, *67*, 2244.
(7) (a) Jayasinghe, L. Y.; Smallridge, A. J.; Trewhella, M. A. *Tetrahedron Lett*. **1993**, *34*, 3949. (b) North, M. *Tetrahedron Lett*. **1996**, *37*, 1699. (c) Rotthaus, O.; Krüger, D.; Demuth, M.; Schaffner, K. *Tetrahedron* **1997**, *53*, 935. (d) Medson, C.; Smallridge, A. J.; Trewhella, M. A. *Tetrahedron Asymmetry* **1997**, *8*, 1049.
(8) (a) Hayakawa, R.; Shimizu, M.; Fujisawa, T. *Tetrahedron: Asymmetry* **1997**, *8*, 3201. (b) Hayakawa, R.; Nozawa, K.; Shimizu, M.; Fujisawa, T. *Tetrahedron Lett*. **1998**, *39*, 67.
(9) Ainsworth, C. *Org. Synth. Coll. Vol*. **1963**, *4*, 536.
(10) Hoffmann, R. W.; Helbig, W.; Ladner, W. *Tetrahedron: Lett*. **1982**, *23*, 3479.
(11) (a) Sato, T.; Fujisawa, T. *Biocatalysis* **1990**, *3*, 1. (b) Hayakawa, R.; Shimizu, M.; Fujisawa, T. *Tetrahedron Lett*. **1996**, *37*, 7533, and the references cited therein.
(12) *syn*-isomer of **4**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42 (s, 3H), 1.45 (s, 3H), 1.64-1.67 (m, 1H), 1.85-1.92 (m, 1H), 2.08 (dq, *J* = 3.05 and 14.65 Hz, 1H), 2.19-2.25 (m, 2H), 2.98 (dt, *J* = 2.44 and 13.43 Hz, 1H), 3.44 (t, *J* = 2.82Hz, 1H), 3.56 (d, *J* = 11.6 Hz, 1H), 4.08 (dd, *J* = 3.05 and 11.6 Hz, 1H), 4.21-4.22 (m, 1H). *anti*-isomer of **4**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (s, 3H), 1.47 (s, 3H), 1.72-1.81 (m, 1H), 1.96-2.04 (m, 1H), 2.07 (ddd, *J* = 3.66, 6.71, and 12.82 Hz, 1H), 2.27-2.31 (m, 1H), 2.38 (dd, *J* = 11.6 and 13.43 Hz, 1H), 2.65 (ddd, *J* = 3.66, 6.10, and 14.04 Hz, 1H), 2.84 (dt, *J* = 2.44 and 13.43 Hz, 1H), 3.54 (dt, *J* = 3.66 and 10.38 Hz, 1H), 3.57 (t, *J* = 11.6 Hz, 1H), 3.68 (dd, *J* = 4.89 and 11.6 Hz, 1H).
(13) (a) Mori, K.; Watanabe, H. *Tetrahedron* **1985**, *41*, 3423. (b) Mori, K.: Nomi, H.; Chuman, T.; Kohno, M.; Kato, K.; Noguchi, M. *Tetrahedron* **1982**, *38*, 3705. (c) Chan, P. C.-M.; Chong, J. M.; Kousha, K. *Tetrahedron* **1994**, *50*, 2703. (d) Miyashita, M.; Toshimitsu, Y.; Shiratani, T.; Irie, H. *Tetrahedron: Asymmetry* **1993**, *4*, 1573.

Article Identifier:
1437-2096,E;1999,0,08,1298,1300,ftx,en;Y10199ST.pdf