Tetrahedron Letters,Vol.27,No.39,pp 4737-4740,1986 0040-4039/86 \$3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

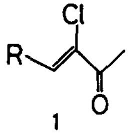
ASYMMETRIC REDUCTION OF Z-3-CHLORO-3-ALKEN-2-ONES WITH FERMENTING BAKER'S YEAST

Masanori Utaka, Satoshi Konishi, and Akira Takeda*
Department of Synthetic Chemistry, School of Engineering,
Okayama University, Tsushima, Okayama 700, Japan

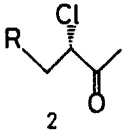
Abstract: Using fermenting baker's yeast, Z-$RCH=CClCOCH_3$ ($R=C_2H_5$, n-C_5H_{11}, n-C_8H_{17}) was reduced initially to (S)-$RCH_2\overset{*}{C}HClCOCH_3$ in 44~84% ee, which was further reduced to $RCH_2\overset{*}{C}HCl\overset{*}{C}HOHCH_3$ in >98% ee with the syn(2S,3S)/anti(2S,3R) ratios of 2.6~18.3.

The use of fermenting baker's yeast has been shown to provide a versatile chiral reducing agent in organic synthesis.[1] Various prochiral compounds such as β-keto esters[2] and α,β-unsaturated ketones[3] have been studied rather extensively and the scope of the asymmetric reduction has been presented in some detail. However, there have been reported relatively few works concerning halo ketones[4] or halo olefins[5] in spite of the fact that these halo compounds are used frequently in organic synthesis.

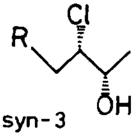
We here report the asymmetric reduction of Z-3-chloro-3-alken-2-ones (1) with fermenting baker's yeast. It produces initially optically active α-chloro ketones (2) which are then reduced to optically pure chlorohydrins (3). The results are shown in Tables 1~3. The reduction is exemplified by the following procedure. To 300 mL of boiled water containing 1.5 g of $CaCO_3$, 0.6g of KH_2PO_4, 0.6 g of $NH_4H_2PO_4$, and 0.3 g of $MgSO_4$, were added 11.4 g of dry baker's yeast (Nisshin) and 20 g of glucose. After the suspension was stirred for 30 min at 33°C, 321 mg (1.84 mmol) of Z-3-chloro-3-nonen-2-one (1b)[6] was added and the stirring was continued for 2 h. The pH of the solution changed from 7 to 5 during the reaction. The mixture was filtered after stirring with 25 g of Celite. The filtrate and the Celite were extracted with ether and the combined extracts were dried ($MgSO_4$) and evaporated to give 1.13 g of a crude oil which was passed through a silica gel column (Merck 60, 30 g; hexane—ether 80:1~20:1) to give 92 mg (28%) of α-chloro ketone (2b)[7] and 108 mg (33%) of chlorohydrin (3b).[7] The optical purity of 2b was determined to be 82% ee by ^1H NMR using

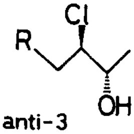

1

a R = C_2H_5
b R = n-C_5H_{11}
c R = n-C_8H_{17}


2

(S)-
44~84% ee


syn-3


anti-3

syn(2S,3S) : anti(2S,3R)
= 2.6~18.3 : 1
>98% ee

Table 1. Reduction of Z-3-Chloro-3-nonen-2-one (**1b**) to 3-Chloro-2-nonanone (**2b**) and 3-Chloro-2-nonanol (**3b**) with Fermenting Baker's Yeast

Dry baker's yeast[a]	Time	**1b**	**2b**	**3b**
g	h	Recovered/%	Yield/%	Yield/%
3	1	48	10	0
3	6	13	26	4
6	6	0	33	20
6	12	0	16	31

a) The amount of **1b** used was 300 mg (1.8 mmol) for each run.

Table 2. Formation of α-Chloro Ketone (**2**) from α,β-Unsaturated α-Chloro Ketone (**1**) with Fermenting Baker's Yeast

Substrate[a]	Time	Product	Yield	$[\alpha]_D$	(c, $CHCl_3$)	ee[b]
	h		%	deg		%
1a	3	**2a**	19[c]	-12.9	(0.99)	44
1b	2	**2b**	28[d]	-36.8	(1.12)	82
1c	2	**2c**	47	-26.6	(1.38)	84

a) For 1.8 mmol of **1**, 12 g of dry yeast was used. b) Determined by ^{1}H NMR using Eu(hfc)$_3$. c) The low yield can be attributed to losses due to volatility of **2a**. Chlorohydrin (**3a**) was also isolated in 10% yield. d) Chlorohydrin (**3b**) was isolated in 33% yield.

Table 3. Formation of Chlorohydrin (**3**) from α,β-Unsaturated α-Chloro Ketone (**1**) with Fermenting Baker's Yeast

Substrate[a]	Time	Product	Yield	syn:anti		$[\alpha]_D$	(c, $CHCl_3$)	ee[b]
	h		%			deg		%
1a	48	**3a**	50	syn	2.6	-35.0	(2.37)	>98
				anti	1	+42.1	(0.84)	>98
1b	48	**3b**	61	syn	8.1	-33.4	(1.15)	>98
				anti	1	+26.6	(0.70)	>98
1c	48	**3c**	22[c]	syn	18.3	-29.1	(1.27)	>98
				anti	1			

a) For 1.8 mmol of **1**, 12 g of dry yeast was used. b) Determined by ^{1}H NMR using Eu(hfc)$_3$. c) The yield of **2c** was 15%.

Eu(hfc)$_3$.[8] The chlorohydrin (**3b**) contained syn and anti isomers[9] in a ratio of 8.1:1, which were separated by HPLC (Yanapak SA-I, hexane–AcOEt 20:1). The optical purities of syn-**3b** and anti-**3b** were also determined to be 98% ee by ^{1}H NMR using Eu(hfc)$_3$.[10]

The reduction was found to produce α-chloro ketone (**2**) initially as indicated in Table 1. This result does not agree with the fact[1a,5] that, in the conjugated system, reduction of the carbonyl group precedes the reduction of carbon—carbon double bond when electronegative substituents, such as halogens, are introduced into the double bond. Interestingly, the reduction of the C=C bond is relatively fast and seems not to depend on the length of carbon chain, while that of the C=O bond is slow and retarded as the carbon-chain length becomes longer. In Table 2, **2c** was obtained in 47% yield within 2 h while **3c** was not obtained at all within 2 h. It took 48 h to produce **3c** in 22% yield.

The stereochemistry of the reduction deserves discussion in detail. It is very important that all the chlorohydrins (**3a**,**b**,**c**), either syn or anti, were virtually optically pure (Table 3). This means that the carbonyl group of α-chloro ketones (**2a**,**b**,**c**) was reduced with a complete enantioselectivity irrespective of the configuration of adjacent chlorine-bearing carbon. Thus, the syn: anti ratio of **3** should be equal to the enantiomer ratio of **2**. The % ee for **2a** is calculated to be 44 by using the syn:anti ratio of **3a**, which is in good agreement with 44% ee observed. Similarly, the calculated and the observed % ee values are 78 and 82 for **2b** and 89 and 84 for **2c**, respectively.

The configuration of optically active α-chloro ketone (**2**) was determined as (S) after conversion of **2b** to 3-chloro-2-methyl-2-nonanol by comparing the sign of optical rotation with that of a reference compound derived from L-(+)-norleucine.[11] This leads to determination of the configuration of optically pure syn- and anti-chlorohydrin (**3**) as (2S,3S) for the syn and (2S,3R) for the anti isomers. Then it is concluded that the carbonyl group of α-chloro ketones (**2**) was reduced to yield the alcohol (**3**) of the (S) configuration, in accordance with that expected from the Prelog rule.[1a,d,f]

Acknowlegement. This work was supported by a Grant-in-Aid for Special Project Research (No. 60119001) from the Ministry of Education, Science and Culture of Japan.

References and Notes

1. (a) C. J. Sih and J. P. Rosazza in "Applications of Biochemical Systems in Organic Chemistry," eds. J. B. Jones, C. J. Sih, and D. Perlman, Wiley, New York (1976), Part 1, Chap. III. (b) A. Fischli in "Modern Synthetic Methods," ed. R. Scheffold, Salle-Sauerländer, Frankfurt (1980), Vol. 2. (c) T. Sugai and K. Mori in "Koso Kino To Seimitsu Yuki Gosei," (Enzyme Functions and Highly Selective Organic Synthesis), ed. M. Ohno, CMC, Tokyo (1984), Chap. 2. (d) S. Kurozumi in Ibid., Chap. 3. (e) T. Oishi and H. Akita in Ibid., Chap. 4. (f) C. J. Sih and C.-S. Chen, Angew. Chem. Int. Ed. Engl., **23**, 570 (1984).
2. Recent papers: T. Fujisawa, T. Ito, and T. Sato, Tetrahedron Lett., **25**, 5083 (1984). K. Nakamura, K. Ushio, S. Oka, and A. Ohno, Ibid., **25**, 3979 (1984). C. Fuganti and F. Grasselli, Ibid., **26**, 101 (1985). T. Kitamura and K. Mori, Ibid., **26**, 451 (1985). W.-R. Shieh, A. S. Gopalan, and C. J. Sih, J. Am. Chem. Soc., **107**, 2993 (1985). K. Nakamura, M. Higaki, K. Ushio, S. Oka, and A. Ohno, Tetrahedron Lett., **26**, 4213 (1985).
3. Recent papers: M. Desrut, A. Kergomard, M. F. Renard, and H. Veschambre,

Tetrahedron, 37, 3825 (1981). A. Kergomard, M. F. Renard, and H. Veschambre, J. Org. Chem., 47, 792 (1982). M. Desrut, A. Kergomard, M. F. Renard, H. Veschambre, Biochem. Biophys. Res. Commun., 110, 908 (1983).

4. P. Santomauro, Biochem. Z., 151, 48 (1924). H. K. Sen, Ibid., 151, 51(1924). R. D. Ridley and M. Stralow, J. Chem. Soc., Chem. Commun., 1975, 400. R. L. Crumbie, D. D. Ridley, and G. W. Simpson, Ibid., 1975, 315. M. Imuta and H. Ziffer, J. Org. Chem., 43, 4540 (1978). M. Imuta, K. Kawai, and H. Ziffer, Ibid., 45, 3352 (1980). T. Kitazume and N. Ishikawa, Chem. Lett., 1984, 587.

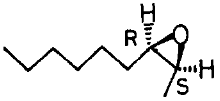
5. C. J. Sih, J. B. Heather, R. Sood, P. Price, G. Peruzzotti, L. F. H. Lee, and S. S. Lee, J. Am. Chem. Soc., 97, 865 (1975). H. J. Ringold, Proc. Int. Congr. Hormonal Steroids, 1st., 1964, 305.

6. The substrates 1 were prepared according to the method reported in S. Tusboi, T. Uno, and A. Takeda, Chem. Lett., 1978, 1325. The Z isomers were obtained by distillation.

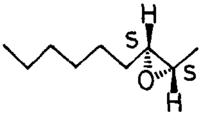
7. Identified by spectral and elemental analyses.

8. The racemic 2b prepared by reduction of 1b with H_2/Pd-C was used as a reference compound. The % ee was determined by using the signal for the methyl group of the carbonyl moiety, which appeared at δ 8.58 and 8.70 for racemic 2b in the presence of 100 mol% $Eu(hfc)_3$ in CCl_4.

9. Identified by spectral and elemental analyses. Both the chlorohydrins were converted to the epoxides by treatment with MeONa. The epoxide having $J_{H,H}$= 4.2 Hz was assigned to the cis isomer which is derived from the syn-chlorohydrin and that having $J_{H,H}$= 2.1 Hz to the trans isomer from the anti-chlorohydrin.



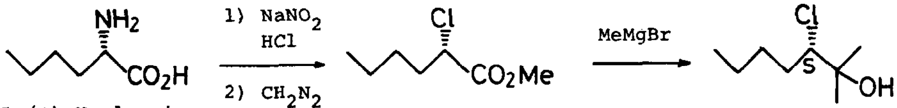
$J_{H,H}$= 4.2 Hz



$J_{H,H}$= 2.1 Hz

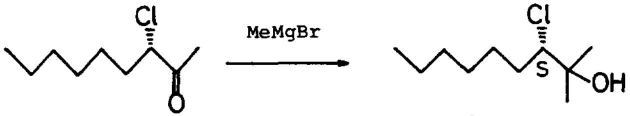
10. The racemic 3b was prepared by reduction of 1b with $NaBH_4$ followed by reduction with H_2/Pd-C. The syn and anti isomers were separated by HPLC and used as reference compounds. The % ee was determined by using the signal for the methyl group of the carbinol moiety, which appeared at δ 1.87 and 1.93 for racemic syn-3b and at δ 1.72 and 1.78 for racemic anti-3b in the presence of 10~20 mol% $Eu(hfc)_3$ in $CDCl_3$.

11. The Transformations are shown below.



L-(+)-Norleucine

$[\alpha]_D^{22}$ -57.2° (c 1.38, $CHCl_3$)



$[\alpha]_D^{24}$ -34.1° (c 1.38, $CHCl_3$)

(Received in Japan 6 May 1986)