Asymmetric Reduction of Carbon-Carbon Double Bonds of Conjugated Enones with Fermenting Bakers' Yeast

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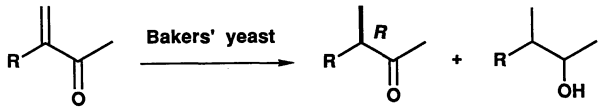
Synopsis. Bakers' yeast reduction of α-substituted or β,β-disubstituted α,β-unsaturated ketones gave saturated chiral ketones with excellent optical purity, while the β,β-disubstituted derivative remained intact.

A number of bakers' yeast reductions of carbon–carbon double bonds, which are functionalized with hydroxymethyl,[1a] formyl,[1b] or nitro group,[1c] have been reported.[1d] However, less attention has been paid on the conjugated enones. For example, the carbonyl group of 4-phenyl-3-buten-2-one is reduced predominantly to give the corresponding (*S*)-allyl alcohol.[2] In contrast, we previously reported the bakers' yeast reduction of the carbon-carbon double bond of functionalized enones such as 3-chloro-3-alken-2-ones[3a] and 3-(1-hydroxyalkyl)-3-buten-2-ones,[3b] both of which afforded the corresponding saturated ketones with high optical purity. The effects of the chloro or the hydroxyl group on the reaction were obscure. We report here the reduction of simple enones such as 3-alkyl-3-buten-2-ones and 3- or 4-phenyl-3-buten-2-one. The α-substituted enones are reduced to the saturated ketones with excellent optical purity. The results are discussed as compared with those of 3-(1-hydroxyalkyl)-3-buten-2-ones.[3b]

Table 1 shows the reduction of 3-alkyl-3-buten-2-ones (**1a—e**) by use of pressed bakers' yeast (PBY). Enones **1b—d** having an alkyl chain of C_6 to C_{11} gave saturated ketones **2b—d** with high enantiomeric excess (ee) (Scheme 1). (2*S**,3*R**)-3-Methyl-2-alkanols **3b**[4] (1% yield) and **3c**[4] (6% yield) were also isolated as a minor component.[5] The absolute configuration for **2b-d** was assigned to be (*R*) by comparison of the rotation with that for authentic (*R*)-**2b**.[6] Interestingly, the enone **1c** was reduced in 30% yield with a rather shorter reaction time (11 h), while the yield could not be increased further even by extension of the time to 22 h. The shorter-chain homolog **1b** and the longer-chain one **1d** required much prolonged reaction times, 64 h and 90 h respectively, to give **2b** and **2d** in rather lowered yields. The shortest homolog **1a** (R=C_5H_{11}) gave neither reduction product nor substrate recovered. The longest one **1e** (R=$C_{12}H_{25}$) remained intact. Thus the yeast reduction of the enones having α-alkyl group **1** was found to be highly dependent on the length of the α-alkyl chain.

The results mentioned above are in contrast to those for the 3-(1-hydroxyalkyl)-3-buten-2-ones:[3b] 1) 3-Pentyl-3-buten-2-one (**1a**) was not reduced nor recovered at all after 87 h incubation, but the 3-(1-hydroxypentyl)-3-buten-2-one was reduced in 56% yield after 69 h. 2) 3-Hexyl-3-buten-2-one (**1b**) was reduced in 24% yield by 64 h incubation without recovery of the starting enone, but 3-(1-hydroxypentyl)-3-buten-2-one was reduced in 72% yield for 114 h. Thus the 1-hydroxy group in the alkyl substituent seems to enhance the yield and prevent the loss of substrate during the incubation.

The substrate was then replaced to the aromatic



1 2 (2S*,3R*)-3

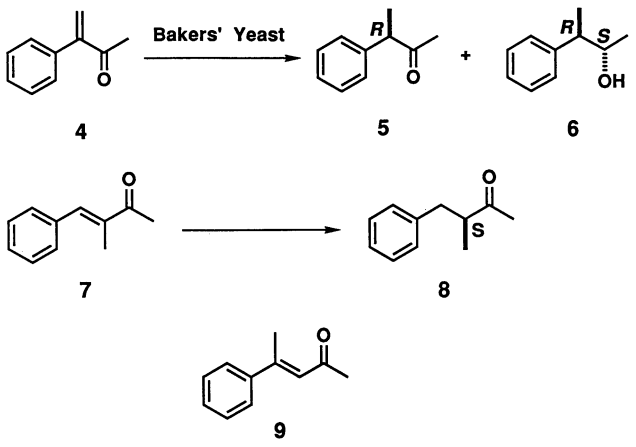
a: R = C_5H_{11}, b: R = C_6H_{13},
c: R = C_8H_{17}, d: R = $C_{11}H_{23}$
e: R = $C_{12}H_{25}$

Scheme 1.

Table 1. Bakers' Yeast Reduction of 3-Alkyl-3-buten-2-ones (**1a—e**)

	1	Time	**1**	(*R*)-**2**		
	R	h	Recovery/%	Yield/%	$[\alpha]_D$ (*c*, $CHCl_3$)	ee[a]/%
a	C_5H_{11}	87	0	0	—	—
b	C_6H_{13}	16	26	15	—	—
b	C_6H_{13}	25	18	16	—	—
b	C_6H_{13}	64	0	24[b]	−15.7° (1.4)[c]	>99
c	C_8H_{17}	11	5	30	—	—
c	C_8H_{17}	22	0	29[d]	−16.4° (2.8)	>98
d	$C_{11}H_{23}$	20	30	13	—	—
d	$C_{11}H_{23}$	50	34	21	—	—
d	$C_{11}H_{23}$	90	20	22	−12.7° (1.3)	>98
e	$C_{12}H_{25}$	74	78	0	—	—

a) Determined by 200 MHz (for **2b**) or 100 MHz (for **2c** and **2d**) ^1H NMR spectra in the presence of (+)-Eu $(hfc)_3$. b) Alcohol **3b** was obtained in 1% yield. c) Reported rotation: $[\alpha]_D$ −12.03°. (neat) for the (*R*) enantiomer (99% ee) (Ref. 6b). d) Alcohol **3c** was produced in 6% yield.



Scheme 2.

analogues. The reduction of 3-phenyl-3-buten-2-one (**4**) was carried out by use of immobilized bakers' yeast (IMBY) to afford (*R*)-(−)-3-phenyl-2-butanone (**5**)[7] (24% yield, 95% ee) and (2*S*,3*R*)-(+)-3-phenyl-2-butanol (**6**)[8] (6% yield) (Scheme 2). The IMBY method required 30 times as much bakers' yeast as the substrate by weight, showing a sharp contrast to the free bakers' yeast method which needed 110 times yeast to give **5** in only 4% yield with 56% ee. The substrate **4** showed a remarkable inhibitory feature to the fermentation.

The reduction of 3-methyl-4-phenyl-3-buten-2-one (**7**) with IMBY gave (*S*)-(+)-3-methyl-4-phenyl-2-butanone (**8**) in 52% yield. However, the optical purity was lowered to 72% ee. The β,β-disubstituted enone such as 4-phenyl-3-penten-2-one (**9**) was recovered unchanged. Thus, the bakers' yeast reduction is found to suffer with the β-substituent(s) of the α,β-unsaturated ketones.

Experimental

Ir spectra were recorded with a Jasco A-102 spectrometer. ^{1}H NMR spectra at 60 and 100 MHz were obtained on JEOL PMX-60SI and JEOL FX-100 spectrometers, respectively, and those at 200 and 500 MHz as well as ^{13}C NMR spectra (50 MHz) were measured on Varian VXR spectrometers. Preparative column chromatography was carried out by using silica gel (Merck Silica Gel 60). Purification by HPLC was performed by use of Hitachi 655 apparatus with Unisil Q column (10.7 mm i.d.×250 mm l). Compounds **7**[9] and **9**[10] were prepared by the reported methods. Elemental analyses were carried out by Eiichiro Amano of this laboratory.

3-Alkyl-3-buten-2-ones (1a—e). These compounds were prepared by the palladium-catalyzed decarboxylation–deacetoxylation of allyl α-acetoxymethyl β-keto carboxylates which were derived from allyl acetoacetate via three steps[11] (method A). Enone **1b** was also synthesized by the formaldehyde-K_2CO_3 promoted deacetylation–methylenation[12] of 3-hexyl-2,4-pentanedione (95% yield), which was prepared by Bu_4NHSO_4 catalyzed alkylation[13] of acetylacetone with 1-iodohexane (70% yield) (method B). The overall yields of **1a—e** (method A) after purification by column chromatography and their spectral and physical data are shown below.

3-Pentyl-3-buten-2-one (1a):[11] 24.9% yield; IR (neat) 1680, 1630 cm^{-1}; ^{1}H NMR (CCl_4) δ=0.75—1.10 (m, 3H), 1.10—2.24 (m, 8H), 2.24 (s, 3H), 5.61 (s, 1H), 5.85 (s, 1H).

3-Hexyl-3-buten-2-one (1b):[14a] 5.6% yield; IR (neat) 1680, 1630 cm^{-1}; ^{1}H NMR (CCl_4) δ=0.65—1.05 (m, 3H), 1.09—1.90 (m, 14H), 2.23 (s, 3H), 5.60 (s, 1H), 5.83 (s, 1H).

3-Octyl-3-buten-2-one (1c):[14b] 22% yield; IR (neat) 1680, 1630 cm^{-1}; ^{1}H NMR (CCl_4) δ=0.70—1.15 (m, 3H), 1.10—1.80 (m, 14H), 2.22 (s, 3H), 5.57 (s, 1H), 5.81 (s, 1H).

3-Undecyl-3-buten-2-one (1d):[14c] 9.7% yield; IR (neat) 1680, 1630 cm^{-1}; ^{1}H NMR (CCl_4) δ=0.70—1.07 (m, 3H), 1.07—1.90 (m, 14H), 2.24 (s, 3H), 5.61 (s, 1H), 5.84 (s, 1H).

3-Dodecyl-3-buten-2-one (1e): 10.5% yield; bp 160 °C (7.5 mmHg, 1 mmHg=133.322 Pa); IR (neat) 1680, 1620 cm^{-1}; ^{1}H NMR (CCl_4) δ=0.70—1.07 (m, 3H), 1.07—1.90 (m, 14H), 2.24 (s, 3H), 5.61 (s, 1H), 5.84 (s, 1H). Found: C, 80.32; H, 12.45%. Calcd for $C_{15}H_{28}O$: C, 80.29; H, 12.58%.

Typical Reduction of 1a—e with Pressed Bakers' Yeast. (*R*)-(−)-3-Methyl-2-undecanone (2c) and (2*S,3*R**)-3-Methyl-2-undecanol (3c):**[4] To a 500 ml round bottomed flask were added boiled water (110 ml), pressed bakers' yeast (7.0 g), and glucose (10.0 g). The suspension was stirred for 20 min at 30 °C and then enone **1c** (275 mg, 1.51 mmol) was added. After stirring for additional 7 h at 30 °C, glucose (10 g) was added and the stirring was continued for 22 h in total. Celite (12 g) was added and the mixture was stirred further for 6 h. After filtration under suction, the filtrate was extracted with ethyl acetate and the residue was washed with ethyl acetate. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Fractionation of the crude products with column chromatography on silica gel (30 g, hexane:ethyl acetate=30:1) followed by purification by HPLC (hexane:ethyl acetate 30:1, 1.7 ml min^{-1}) gave ketone **2c** (3.5 min, 80 mg, 29% yield) and alcohol **3c** (7.0 min, 16 mg, 6% yield).

2c: IR (neat) 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.70—2.02 (m, 17H), 1.07 (d, 3H, *J*=7 Hz), 2.09 (s, 3H), 2.01—2.60 (m, 1H); ^{13}C NMR ($CDCl_3$) δ=14.1 (q), 16.2 (q), 22.7 (t), 27.3 (t), 28.0 (q), 29.3 (t), 29.5 (t), 29.7 (t), 31.9 (t), 47.3 (d), 212.9 (s). Found: C, 78.44; H, 13.34%. Calcd for $C_{12}H_{24}O$: C, 78.20; H, 13.12%.

3c:[4] IR (neat) 2800—3000 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ= 0.84 (d, 3H, *J*=6.0 Hz), 0.85 (t, 3H, *J*=7.0 Hz), 1.10—1.60 (m, 15H), 1.10 (d, 3H, *J*=6.5 Hz); 3.63 (dq, 1H, *J*=6.0 and 6.0 Hz); ^{13}C NMR ($CDCl_3$) δ=14.1 (q), 14.5 (q), 19.3 (q), 22.7 (t), 27.3 (t), 29.4 (t), 29.7 (t), 30.0 (t), 31.9 (t), 32.6 (t), 40.1 (d), 71.8 (d). Found: C, 77.42; H, 14.01%. Calcd for C: 77.35; H, 14.06%.

(*R*)-(−)-3-Methyl-2-nonanone (2b)[6] **and (2*S**,3*R**)-3-Methyl-2-nonanol (3b).**[15] **2b:** IR (neat) 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.86 (t, 3H, *J*=6.8 Hz), 1.06 (d, 3H, *J*=6.8 Hz), 1.25 (m, 10H), 2.11 (s, 3H); 2.48 (dq, 1H, *J*=6.8 Hz and 6.8 Hz).

3b: 1% yield; ^{1}H NMR ($CDCl_3$) δ=0.87 (d, 3H, *J*=6.6 Hz), 0.89 (bt, 3H), 1.13 (d, 3H, *J*=6.3 Hz), 1.05—1.70 (m, 11H), 3.67 (dq, 1H *J*=6.0 and 6.0 Hz).

(*R*)-(−)-3-Methyl-2-tetradecanone (2d): IR (neat) 1715 cm^{-1}; ^{1}H NMR ($CDCl_4$) δ=0.70—1.90 (m, 23H), 1.03 (d, 3H, *J*=7 Hz), 2.01 (s, 3H), 2.01—2.65 (m, 1H). Found: C, 79.41; H, 13.33%. Calcd for $C_{15}H_3O$: C, 79.58; H, 13.35%.

Determination of ee for (*R*)-2b—d. The ee of **2b** was determined by use of the ^{1}H NMR (200 MHz, $CDCl_3$) spectrum recorded in the presence of 30 mol% of (+)-Eu(hfc)$_3$ at 30 °C. Under the conditions, the singlet due to the terminal methyl group of (±)-**2b**, prepared as described below, resolved to a pair of singlets at δ=3.130 (for *S*) and δ=3.111 (for *R*). Similar ^{1}H NMR (100 MHz) experiments were carried out for **2c** and **2d** by using 50 mol% of (+)-Eu(hfc)$_3$.

Preparation of (±)-2b—d. These compounds were prepared for the references in the ^{1}H NMR shift reagent experiments. A mixture of 3-hexyl-3-buten-2-one (212 mg, 1.37 mmol) and 5% Pd–C (110 mg) was stirred at room temperature under hydrogen atmosphere overnight. Filtra-

tion of the mixture followed by concentration gave a crude product, which was purified by column chromatography (hexane:ethyl acetate=30:1) to give (±)-**2b** in 74% yield. Compounds (±)-**2c** (52% yield) and (±)-**2d** (40% yield) were obtained in a similar way.

3-Phenyl-3-buten-2-one (4).[16] The following method is newly developed here. 1-Phenylvinylmagnesium bromide was prepared by the reaction of α-bromostyrene (2.75 g, 15 mmol) and magnesium turnings (413 mg, 0.017 g-atom) in 10 ml of THF.[17] The dark brown suspension of the Grignard reagent was introduced dropwise to a solution of acetic anhydride (1.53 g, 5 mmol) in 5 ml of THF at −78 °C. After being stirred for 1 h at the temperature, the cooling bath was removed and the mixture was stirred further for 2.5 h. Water was added and the solvent was removed under reduced pressure. The organic layer was extracted with ethyl acetate and washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, concentrated under reduced pressure. The crude product was distilled under vacuum to give 1.40 g (64% yield) of enone **4**: Bp 100—105 °C (5 mmHg); IR (neat) 3070, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.45 (s, 3H), 5.98 (s, 1H), 6.19 (s, 1H), 7.25—7.45 (5H, m); ^{13}C NMR ($CDCl_3$) δ=27.4 (q), 125.7 (t), 128.1 (d), 128.4 (d), 137.0 (s), 149.5 (s), 199.4 (s).

Bakers' Yeast Reduction of Enone (4). (*R*)-(−)-3-Phenyl-2-butanone (5)[7] **and (2*S*,3*R*)-(+)-3-Phenyl-2-butanol (6).**[8] Immobilized bakers' yeast (dry bakers' yeast: sodium alginate= 4:1 in w/w) was prepared by the procedure described previously.[18] To a mixture of the immobilized bakers' yeast (78 ml including 6 g of bakers' yeast), glucose (20 g), and boiled water (150 ml) was stirred at 35 °C for 30 min. Enone **4** (963 mg, 6.59 mmol) was added and the mixture was stirred for 48 h. In the course of the reaction, 110 g of glucose was consumed. The combined ethyl acetate extracts both from the aqueous layer and from the gels were treated in a usual manner[18] and the crude product was purified by column chromatography (hexane:ethyl acetate, 20—10:1) to give ketone **5** (236 mg, 24% yield) and (2*S*,3*R*)-alcohol **6** (55 mg, 6% yield).

5: ($[\alpha]_D$−333° (*c* 0.75, benzene), lit[7] $[\alpha]_D$+368° (benzene) for 3*S*); IR (neat) 3050, 1720, 1500 cm^{-1}, ^1H NMR ($CDCl_3$) δ=1.38 (d, 3H, *J*=7.0 Hz), 2.04 (s, 3H), 3.74 (q, 1H, *J*=7.0 Hz), 7.18—7.36 (m, 5H).

6: ($[\alpha]_D$+17.7° (*c* 3.53, EtOH), [lit,[8] $[\alpha]_D$+16.2 (*c* 3.6, EtOH, 81% ee)]; ^1H NMR ($CDCl_3$) δ=1.23 (d, 3H, *J*=6.2 Hz), 1.26 (d, 3H, *J*=7.2 Hz), 1.58 (s, 1H, OH), 2.67 (dq 1H, *J*=7.2 Hz, 7.2 Hz), 3.85 (dq, 1H, *J*=7.2 Hz, 6.2 Hz), 7.2—7.4 (m, 5H).

Optical purity of **5** was determined as 95% ee in a similar manner to that dscribed for aliphatic ketone **2b-d**.

(±)-3-Phenyl-2-butanone (±)-(5). A mixture of enone **4** (200 mg, 1.37 mmol), palladium chloride (23 mg, 0.13 mmol), silica gel (100 mg) in ethanol (3 ml) was stirred under hydrogen at room temperature for 2 d. A usual workup followed by distillation [bp 100—105 °C (5 mmHg)] gave ketone (±)-**5** (152 mg, 75% yield).

(*S*)-(+)-4-Phenyl-3-methyl-2-butanone (8).[19] Incubation was carried out at 35 °C for 82 h by use of enone **7** (160 mg, 1.88 mmol), glucose (90 g in all), water (400 ml), and the immobilized yeast (150 ml, including 18 g of bakers' yeast). Workup in a usual way followed by purification with preparative TLC (20 cm×20 cm, silica-gel plate with 2 mm thickness, hexane:ether 5:1) gave ketone **8** (110 mg, 37% yield): $[\alpha]_D$+33.6° (*c* 2.74, EtOH) (lit, $[\alpha]_D$+45.5° (EtOH) for **8**); IR (neat) 1710 and 1600 cm^{-1}; ^1H NMR (CCl_4) δ=1.02 (d, 3H, *J*=6 Hz), 1.95 (s, 3H), 2.28—3.10 (m, 3H), 7.05 (s, 5H). Optical purity was determined to be 72% ee by a similar ^1H NMR (200MHz) method to that described above.

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