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Stereochemical Control in Microbial Reduction. XXVIII. Asymmetric Reduction of α,β-Unsaturated Ketones with Bakers' Yeast

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Bakers' yeast reduction of α,β-unsaturated ketones affords optically active saturated ketones contaminated by allylic and saturated alcohols as minor components. Stereoselectivity of the reduction of carbon–carbon double bond strongly depends on the structure of β-aryl substituent. The bakers' yeast reduction of β-phenyl enones gives saturated ketones in moderate stereoselectivity. Stereoselectivity is not altered by substitution at the *para*-position, whereas introduction of a substituent at the *ortho*- or *meta*-position drastically improves the stereoselectivity. Deuterium-labeling experiments reveal that the enzymatic reduction of carbon–carbon double bond proceeds with formal *trans*-addition of hydrogens regardless the efficiency of stereoselectivity. The resulting optically active ketone was converted to the precursor of (*S*)-iopanoic acid, an inhibitor of thyroxine 5′-deiodinase that is a thyroid hormone-converting enzyme and an oral cholecystographic agent.

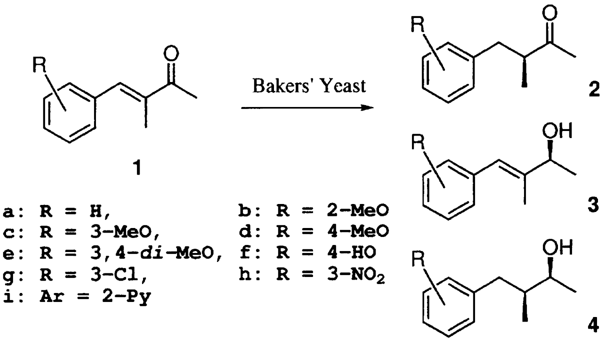
Asymmetric reduction of carbonyl groups with a microbe has been studied thoroughly and utilized widely as a method for preparing chiral secondary alcohols. Bakers' yeast, *Saccharomyces cerevisiae*, is most frequently employed for this purpose.[1,2] On the other hand, less attention has been paid on the reduction of α,β-unsaturated carbonyl compounds.

Stereochemistry of the bakers' yeast reduction of popular carbonyl compounds is predictable to a certain extent by the Prelog rule,[3] whereas that of the reduction of α,β-unsaturated carbonyl compounds mediated by bakers' yeast is unforeseeable and the mode of reduction depends strongly on the structure of C=C double bond. The presence or absence of substituent(s) at the unsaturated carbons is crucial to control the stereochemistry of the reduction. For example, the reduction of α-alkyl or phenyl substituted enones affords the corresponding saturated (*R*)-ketones selectively with high enantiomeric excesses (ee), which is accompanied by the formation of small amounts of the saturated alcohols.[4] α-(1-Hydroxyalkyl) enones are also reduced to the corresponding saturated (*R*)-ketones selectively.[5] In the case of the reduction of an enone substituted by a β-phenyl group, the product is the corresponding (*S*)-allylic alcohol.[6] Recently, it was reported that γ-benzoyloxy enones were transformed into saturated ketones selectively.[7] A β,β-disubstituted enone such as 4-phenyl-3-penten-2-one was recovered unchanged.[4] The reduction of α,β-disubstituted enones such as 3-chloro-3-alken-2-one affords the corresponding saturated ketones and saturated alcohols.[8] On the other hand, the reduction of cyclic α,β-disubstituted enone such as 2-benzylidenecyclohexanone gives a mixture of almost racemic saturated ketone and optically pure unsaturated (*S*)-alcohol.[9]

It is interesting to note that controversial results were obtained from the reduction of an α,β-disubstituted enone such as 3-methy-4-phenyl-3-buten-2-one. Fuganti et al. reported that the reduction of the enone gives the corresponding (*S*)-allylic alcohol (in 15% yield) contaminated by small amounts of the saturated alcohol,[10] whereas Sakai et al. reported the production of saturated (*R*)-ketone by the same reaction.[4] The former research group claims that the carbonyl group of the enone is reduced predominantly, whereas the latter group claims that the carbon–carbon double bond is reduced exclusively. Since there remain ambiguities in the mode of the reduction and since the stereoselectivities of these reductions are unsatisfactory, we investigated detailed structural features influencing the mode of bakers' yeast reduction of α,β-disubstituted-α,β-unsaturated carbonyl compounds. Recently, we reported that bakers' yeast reduction of 3-methyl-4-(*ortho*- or *meta*-substituted phenyl)-3-buten-2-one gives the corresponding chiral saturated ketone in excellent stereoselectivity.[11] This paper will describe details in the stereoselective synthesis of chiral ketones. We explain the stereochemical course of the reduction of carbon–carbon double bond by means of deuterium-labelling experiments.

Results and Discussion

The reduction of 3-methyl-4-phenyl-3-buten-2-one (**1a**) with bakers' yeast affords (*S*)-(+)-3-methyl-4-phenyl-2-butanone (**2a**) in 42% yield and 71% ee, in which 3-methyl-4-phenyl-3-buten-2-ol (**3a**) and 3-methyl-4-phenyl-2-butanol (**4a**) were also detected as minor components in 3 and 9% yields, respectively (Eq. 1). The carbon–carbon double bond is reduced predominantly here, which is identical with the result reported by Sakai et al.[4] Although the chemical yield of chiral ketone is modest, stereoselectivity of the product is unsatisfactory under the conditions employed. Therefore, we have tried to improve the stereoselectivity of the reduction.



a: R = H, b: R = 2-MeO
c: R = 3-MeO, d: R = 4-MeO
e: R = 3,4-*di*-MeO, f: R = 4-HO
g: R = 3-Cl, h: R = 3-NO_2
i: Ar = 2-Py

(1)

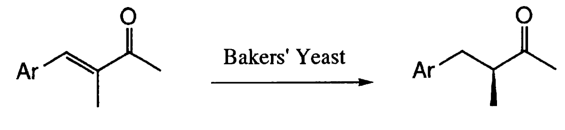
Effect of Substrate Concentration on Stereoselectivity. The stereoselectivity of microbial reduction is often dependent upon the substrate concentration.[12—16] Recently, we elucidated the mechanism in enzyme level for the dependence of substrate concentration on stereoselectivity of the reduction by whole yeast cell.[16] This phenomenon becomes prominent when plural competing enzymes with opposite stereochemical preferences and different Michaelis constants, K_m, participate in the reduction in an intact cell. Low substrate concentration is recommended for improvement of enantioselectivity when K_m of the most enantioselective enzyme is smaller than those of the others. With these results in mind, **1a** was subjected to bakers' yeast reduction under various substrate concentrations. The results are summarized in Table 1.The ee was almost constant at 75% in every case, which suggests that only one enzyme participates the reduction of this enone in a yeast cell.

Effect of Substituent on Stereoselectivity. Various β-aryl enones, **1a—i**, were subjected to the reduction with bakers' yeast. The results are listed in Table 2. Bakers' yeast reduction of α,β-disubstituted α,β-unsaturated carbonyl compounds affords the corresponding saturated (*S*)-ketones **2** selectively in every case. The stereoselectivity of the reduction of carbon–carbon double bond is strongly influenced by a substituent on the phenyl ring. The introduction of a hydroxy group, **1f**, for example, retards the reduction rate and decreases the stereoselectivity. In addition, the site of a substituent plays a crucial role in the stereoselectivity of the reduction. The presence of a methoxy substituent at the *para*-position, **1d**, decreases stereoselectivity of the reduction, whereas substitution at the *ortho*- or *meta*-position, **1b** or **1c**, drastically improves the stereoselectivity up to a satisfactory level. Since a substituent at the *ortho*-position retards the reduction rate considerably, a *meta*-substitution affords the most favorable result. The reduction of *meta*, *para*-disubstituted enone **1e** also affords the saturated (*S*)-ketone **2e** in excellent stereoselectivity. Since the introduction of a chloro or nitro group at the *meta*-position, **1g** or **1h**, improves the stereoselectivity similarly, the steric bulk of the substituent at the *ortho*- or *meta*-position has been proven to be more important than its electronic effect.

Table 1. Effect of Substrate Concentration on the Stereoselectivity in the Reduction of 3-Methyl-4-phenyl-3-buten-2-one (**1a**)

Substrate concentration/mM	Time/h	Yield/%	ee/%
30	96	46	75
15	30	42	71
7.5	3.5	12	72
3.0	3.5	14	75
1.5	3.5	29	74
0.3	3	34	76

Table 2. Asymmetric Reduction of Enones, **1**, with Bakers' Yeast

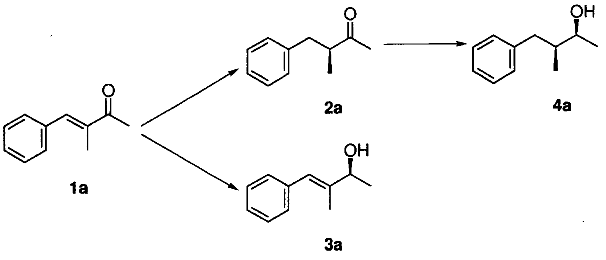


1a-i **2a-i**

	Ar	Time/h	Yield/%	ee/%
a	ph	30	42	71
b	2-MeO-C_6H_4	48	13	>95
c	3-MeO-C_6H_4	48	72	>95
d	4-MeO-C_6H_4	20	73	61
e	3,4-*di*-MeO-C_6H_4	60	59	>95
f	4-HO-C_6H_4	76	20	58
g	3-Cl-C_6H_4	24	91	96
h	3-NO_2-C_6H_4	48	49	>95
i	2-Py	50	59	65

Absolute configurations of the products were determined as follows. Since optical rotations of authentic (*S*)-**2a** and (*R*)-**2e** have been reported, it is elucidated without ambiguity that **2a** and **2e** obtained from the bakers' yeast reduction as the products have the *S* configuration.[4,17] The major enantiomers of yeast reduction products are always the ones that have longer retention times in a chiral capillary GLC. These facts, together with the structural resemblance, suggest that the product ketones **2** have the same absolute configuration of *S*.

Reaction Pathways Giving Products. In order to elucidate the reaction pathway giving three species of products, **2**, **3**, and **4**, a racemic saturated ketone **2a** and a racemic allylic alcohol **3a** were prepared and subjected to the bakers' yeast reduction. The saturated ketone **2a** was further reduced giving a saturated alcohol **4a** but slowly, whereas the allylic alcohol **3a** was recovered unchanged (Eq.2). The results suggest that **4** is afforded through **2** after a prolonged reaction time or under stronger reaction conditions, whereas **3** is an end-product which is formed through a different path from that to **2** (Eq.2).

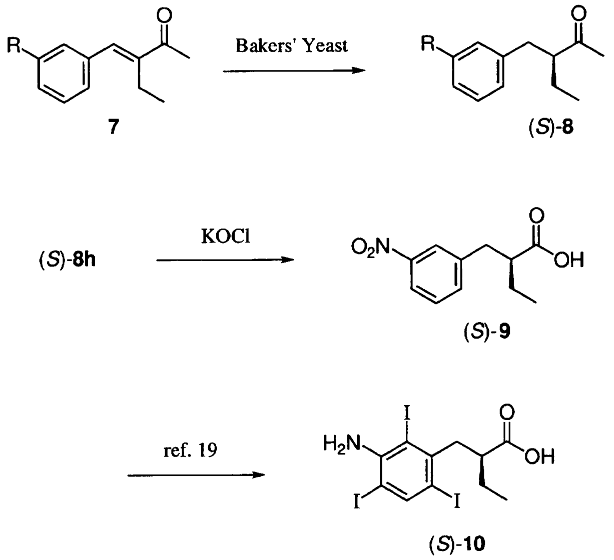


(2)

Stereochemical Course for the Reduction of C=C Dou-

ble Bond. The stereochemical course of the enzymatic reduction of carbon–carbon double bond in the enone is particularly interesting. Stereospecificity of the hydrogenation was monitored by ^{1}H NMR analysis of the diastereotopic methylene protons in the reduction product of deuterium-labelled enone **1a**-4-*d* and **1e**-4-*d*. The ^{1}H NMR spectrum of non-deuterated **2e** exhibits two signals at 2.52 and 2.94 ppm assignable to the diastereotopic methylene protons (Fig. 1a). The *cis*-hydrogenation product **2e**-4-*d* which was prepared independently by catalytic hydrogenation of **1e**-4-*d* by Pd/C shows one doublet at 2.94 ppm (Fig. 1b). The product from the bakers' yeast reduction shows one doublet at 2.52 ppm (Fig. 1c) in contrast to the spectrum of the *cis*-hydrogenation product. The result reveals that the enzymatic reduction proceeds with formal *trans*-addition of the hydrogens. Similar experiments were performed with respect to **1a**-4-*d* which was reduced by bakers' yeast with only low stereoselectivity, and the same result was obtained. Consequently, the enzymatic reduction of carbon–carbon double bond in the enone proceeds with 100% formal *trans*-addition of hydrogens even when the reduction is accompanied by low stereoselectivity. The finding reveals that the low stereoselectivity stems from random positioning of the substrate in the pocket of enzyme instead of random stereochemistry of hydrogenation.

Synthesis of a Precursor for (*S*)-Iopanoic Acid. α-Ethyl analogs of the enones, 3-ethyl-4-phenyl-3-buten-2-one (**7a**) and 3-ethyl-4-(3-nitrophenyl)-3-buten-2-one (**7h**), are also reduced with bakers' yeast giving (*S*)-ketones **8a** and **8h** in more than 98% ee. Although the yeast reduction of **7h** in a larger scale affords the product in lower yield, the stereoselectivity remains unaltered. α-Ethyl substitution of the enone improves the stereoselectivity up to satisfactory level. Haloform reaction of **8h** with potassium hypochlorite gives an (*S*)-acid **9** without racemization.[18] The absolute configuration of **9** was determined to be *S* by comparing its optical rotation with that reported.[19] The (*S*)-acid **9** is a synthetic precursor for iopanoic acid (*S*)-**10**, (*S*)-(+)-3-(3-amino-2,4,6-triiodophenyl)-2-ethylpropionic acid, an inhibitor of thyroxine 5′-deiodinase that is a thyroid hormone-converting enzyme,[20] and an oral cholecystographic agent (Eq.3).[19]



(3)

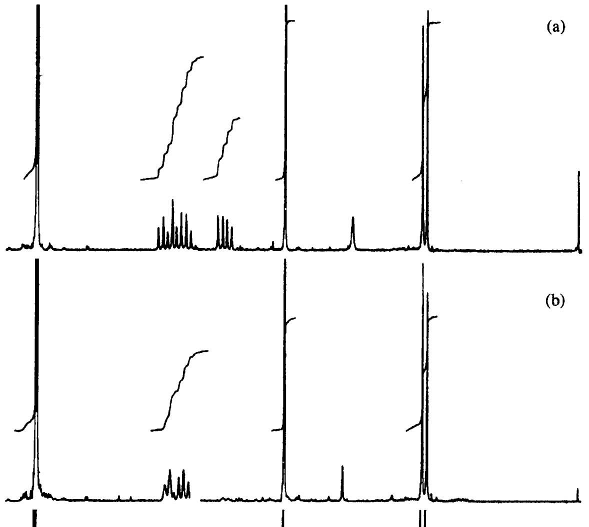


Fig. 1. Expanded region of the ^{1}H NMR spectra of (a) **2e**, (b) **2e**-4-*d* obtained by hydrogenation of **1e**-4-*d* by Pd/C, and (c) **2e**-4-*d* obtained by bakers' yeast reduction of **1e**-4-*d*.

Experimental

Instruments. NMR spectra were recorded on a Varian VXR-200 spectrometer in $CDCl_3$ solutions with tetramethylsilane (TMS) as an internal reference. Infrared spectra were collected on a JASCO FT/IR-5300 spectrometer. Optical rotations were measured on a JASCO DIP-181 digital polarimeter. Elemental analyses were performed with a Yanaco MT-5 Elemental Analyzer. Gas chromatograms were recorded on a Shimadzu GC-14B (OV-1701 Bonded, 25 m) and GC-9A (Chiraldex G-TA, 30 m) gas chromatographs.

Materials. Organic reagents and solvents were purchased from Nacalai Tesque, Inc., Wako Pure Chemical Ind., Ltd., and Aldrich Chemical Co. Bakers' yeast was purchased from Oriental Yeast Co. and stored in a refrigerator.

4-Aryl-3-methyl-3-buten-2-ones (1a—i). A slight modification of the reported method was adopted for the synthesis of these compounds.[21] In a 50 mL flask, 20 mL of acetic acid, 3.6 g (50 mmol) of 2-butanone, and 25 mmol of the corresponding aromatic aldehyde were placed, then the solution was stirred at room temperature. To the solution, 2.4 g of H_2SO_4 was added slowly. After 20 h, the reaction mixture was poured onto 100 mL of water, neutralized with 25% aqueous NaOH, and extracted with 100 mL of ether. The ether solution was washed with aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure.

The residue was purified by column chromatography on silica gel with hexane/ethyl acetate (5/1: v/v) as an eluent to obtain 4-aryl-3-methyl-3-buten-2-one. The yields of the isolated products and their spectral as well as physical data are listed below.

3-Methyl-4-phenyl-3-buten-2-one (1a): 85% yield; ^{1}H NMR ($CHCl_3$) δ=2.06 (3H, d, J=1.4 Hz), 2.47 (3H, s), 7.31—7.44 (5H, m), 7.53 (1H, d, J=1.4 Hz); IR (neat) 1667 cm^{-1}. Found: C, 82.33; H, 7.54%. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55%.

4-(2-Methoxyphenyl)-3-methyl-3-buten-2-one (1b): 48% yield; ^{1}H NMR ($CHCl_3$) δ=1.99 (3H, d, J=1.4 Hz), 2.48 (3H, s), 3.88 (3H, s), 6.91—7.03 (2H, m), 7.31—7.39 (2H, m), 7.72 (1H, s); IR (neat) 1667 cm^{-1}. Found: C, 75.73; H, 7.42%. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42%.

4-(3-Methoxyphenyl)-3-methyl-3-buten-2-one (1c): 38% yield; ^{1}H NMR ($CHCl_3$) δ=2.06 (3H, d, J=1.2 Hz), 2.47 (3H, s), 3.84 (3H, s), 6.87—7.03 (3H, m), 7.34 (1H, dd, J=7.8, 8.0 Hz), 7.49 (1H, s); IR (neat) 1667 cm^{-1}. Found: C, 75.60; H, 7.50%. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42%.

4-(4-Methoxyphenyl)-3-methyl-3-buten-2-one (1d): 32% yield; ^{1}H NMR ($CHCl_3$) δ=2.07 (3H, d, J=1.4 Hz), 2.45 (3H, s), 3.85 (3H, s), 6.92—6.98 (2H, m), 7.39—7.44 (2H, m), 7.48 (1H, s); IR (neat) 1661 cm^{-1}. Found: C, 75.55; H, 7.52%. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42%.

4-(3,4-Dimethoxyphenyl)-3-methyl-3-buten-2-one (1e): 29% yield; ^{1}H NMR ($CHCl_3$) δ=2.09 (3H, d, J=1.4 Hz), 2.46 (3H, s), 3.92 (3H, s), 3.93 (3H, s), 6.92 (1H, d J=8.4 Hz), 6.98 (1H, d, J=2.0 Hz), 7.07 (1H, dd, J=2.0, 8.4 Hz), 7.47 (1H, s); IR (neat) 1659 cm^{-1}. Found: C, 70.57; H, 7.32%. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32%.

4-(4-Hydroxyphenyl)-3-methyl-3-buten-2-one (1f): 55% yield; ^{1}H NMR ($CHCl_3$) δ=2.08 (3H, d, J=1.2 Hz), 2.47 (3H, s), 6.21 (1H, br), 6.92 (2H, d, J=8.6 Hz), 7.38 (2H, d, J=8.6 Hz), 7.50 (1H, s); IR (neat) 1640, 3252 cm^{-1}. Found: C, 74.90; H, 6.92%. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86%.

4-(3-Chlorophenyl)-3-methyl-3-buten-2-one (1g): 97% yield; ^{1}H NMR ($CHCl_3$) δ=2.04 (3H, d, J=1.4 Hz), 2.46 (3H, s), 7.25—7.43 (5H, m); IR (neat) 1669 cm^{-1}. Found: C, 67.69; H, 5.70%. Calcd for $C_{11}H_{11}OCl$: C, 67.87; H, 5.70%.

3-Methyl-4-(3-nitrophenyl)-3-buten-2-one (1h): 51% yield; ^{1}H NMR ($CHCl_3$) δ=2.07 (3H, d, J=1.4 Hz), 2.49 (3H, s), 7.52 (1H, s), 7.61 (1H, dd, J=7.8, 8.0 Hz), 7.73 (1H, d, J=7.8 Hz), 8.18—8.24 (1H, m), 8.28 (1H, s); IR (KBr) 1672, 1524, 1354 cm^{-1}. Found: C, 64.45; H, 5.29; N, 6.85%. Calcd for $C_{12}H_{13}NO_3$: C, 64.38; H, 5.40; N, 6.83%.

3-Methyl-4-(2-pyridyl)-3-buten-2-one (1i): 36% yield; ^{1}H NMR ($CHCl_3$) δ=2.22 (3H, d, J=1.4 Hz), 2.49 (3H, s), 7.20—7.28 (1H, m), 7.45 (1H, d, J=7.8 Hz), 7.50 (1H, d, J=1.4 Hz), 7.75 (1H, ddd, J=1.8, 7.6, 7.8), 8.69—8.72 (1H, m); IR (neat) 1669 cm^{-1}. Found: C, 74.42; H, 6.96; N, 8.74%. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69%.

General Procedure for Yeast Reduction of Enone 1 and 7. To a stirred suspension of dried bakers' yeast (5 g) in 30 mL of tap water, 0.5 mmol of substrate in the least amount of ethanol was added at 35 °C. The reaction was monitored by gas chromatography. After an appropriate reaction time, the reaction mixture was subjected to centrifugal separation (4,000 rpm, 10 min) and the supernatant was extracted with ether. The ether solution was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel with hexane/ethyl acetate (5/1: v/v) as an eluent to obtain 3-alkyl-4-aryl-2-butanone. The chemical yield and ee of each product were determined by using a capillary GC-column, OV-1701 (dodecane as a standard compound) and Chiraldex G-TA, respectively. Results are summarized in Tables 1 and 2. Their spectral and physical data are shown below.

3-Methyl-4-phenyl-2-butanone (2a): 42% yield; ^{1}H NMR ($CHCl_3$) δ=1.09 (3H, d, J=7.0 Hz), 2.09 (3H,s), 2.56 (1H, dd, J=7.4, 13.0 Hz), 2.75—2.92 (1H, m), 3.00 (1H, dd, J=6.8, 13.0 Hz), 7.13—7.33 (5H, m); IR (neat) 1713 cm^{-1}. Found: C, 81.17; H, 8.84%. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70%.

4-(2-Methoxyphenyl)-3-methyl-2-butanone (2b): 13% yield; ^{1}H NMR ($CHCl_3$) δ=1.05 (3H, d, J=7.0 Hz), 2.11 (3H, s), 2.55 (1H, dd, J=7.0, 12.4 Hz), 2.81—3.05 (2H, m), 3.82 (3H, s), 6.83—6.91 (2H, m), 7.06—7.24 (2H, m); IR (neat) 1713 cm^{-1}. Found: C, 74.92; H, 8.40%. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39%.

4-(3-Methoxyphenyl)-3-methyl-2-butanone (2c): 72% yield; ^{1}H NMR ($CHCl_3$) δ=1.09 (3H, d, J=6.8 Hz), 2.10 (3H, s), 2.53 (1H, dd, J=7.2, 13.0 Hz), 2.74—2.92 (1H, m), 2.98 (1H, dd, J=7.2, 13.0 Hz), 3.79 (3H, s), 6.69—6.77 (3H, m), 7.16—7.26 (1H, m); IR (neat) 1713 cm^{-1}. Found: C, 75.15; H, 8.54%. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39%.

4-(4-Methoxyphenyl)-3-methyl-2-butanone (2d): 73% yield; ^{1}H NMR ($CHCl_3$) δ=1.07 (3H, d, J=6.8 Hz), 2.07 (3H, s), 2.51 (1H, dd, J=6.9, 13.0 Hz), 2.70—2.88 (1H, m), 2.93 (1H, dd, J=6.8, 13.0 Hz), 3.77 (3H, s), 6.81 (2H, d, J=8.7 Hz), 7.06 (2H, d, J=8.7 Hz); IR (neat) 1711 cm^{-1}. Found: C, 74.93; H, 8.35%. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39%.

4-(3,4-Dimethoxyphenyl)-3-methyl-2-butanone (2e): 59% yield; ^{1}H NMR ($CHCl_3$) δ=1.09 (3H, d, J=7.0 Hz), 2.09 (3H, s), 2.52 (1H, dd, J=7.0, 12.9 Hz), 2.73—2.89 (1H, m), 2.94 (1H, dd, J=7.0, 12.9 Hz), 3.86 (3H, s), 3.87 (3H, s), 6.67—6.81 (3H, m); IR (neat) 1711 cm^{-1} $[\alpha]^{20}_{D}$ +33.6 (c 4.3, $CHCl_3$). Found: C, 70.47; H, 8.31%. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16%.

4-(4-Hydroxyphenyl)-3-methyl-2-butanone (2f): 20% yield; ^{1}H NMR ($CHCl_3$) δ=1.09 (3H, d, J=7.0 Hz), 2.09 (3H, s), 2.52 (1H, dd, J=6.4, 12.8 Hz), 2.71—2.96 (2H, m), 5.15 (1H, br), 6.74 (2H, d, J=8.5 Hz), 7.01 (2H, d, J=8.5 Hz); IR (neat) 1698, 3376 cm^{-1}. Found: C, 74.08; H, 7.93%. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92%.

4-(3-Chlorophenyl)-3-methyl-2-butanone (2g): 91% yield; ^{1}H NMR ($CHCl_3$) δ=1.10 (3H, d, J=7.0 Hz), 2.11 (3H, s), 2.52 (1H, dd, J=7.4, 13.1 Hz), 2.73—2.90 (1H, m), 2.99 (1H, dd, J=6.6, 13.1 Hz), 7.02—7.06 (1H, m), 7.14—7.22 (3H, m); IR (neat) 1713 cm^{-1}. Found: C, 66.86; H, 6.58%. Calcd for $C_{11}H_{13}OCl$: C, 67.18; H, 6.66%.

3-Methyl-4-(3-nitrophenyl)-2-butanone (2h): 49% yield; ^{1}H NMR ($CHCl_3$) δ=1.15 (3H, d, J=7.0 Hz), 2.14 (3H, s), 2.67 (1H, dd, J=7.2, 13.4 Hz), 2.80—2.97 (1H, m), 3.14 (1H, dd, J=7.0, 13.4 Hz), 7.41—7.53 (2H, m), 8.04—8.11 (2H, m); IR (neat) 1713, 1528, 1352 cm^{-1}. Found: C, 63.87; H, 6.36; N, 6.61%. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76%.

3-Methyl-4-(2-pyridyl)-2-butanone (2i): 59% yield; ^{1}H NMR ($CHCl_3$) δ=1.13 (3H, d, J=6.8 Hz), 2.17 (3H, s), 2.74 (1H, dd, J=9.6, 16.4 Hz), 3.10—3.25 (2H, m), 7.07—7.15 (2H, m), 7.58 (1H, ddd, J=1.8, 7.6, 7.8 Hz), 8.50—8.53 (1H, m); IR (neat) 1713 cm^{-1}. Found: C, 73.08; H, 8.11; N, 8.39%. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58%.

3-Ethyl-4-phenyl-2-butanone (8a): 58% yield; ^{1}H NMR ($CHCl_3$) δ=0.89 (3H, t, J=7.4 Hz), 1.41—1.72 (2H, m), 2.01 (3H, s), 2.63—2.92 (3H, m), 7.12—7.32 (5H, m); IR (neat) 1713 cm^{-1}. Found: C, 81.70; H, 9.27%. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15%.

3-Ethyl-4-(3-nitrophenyl)-2-butanone (8h): 99% yield; ^{1}H NMR ($CHCl_3$) δ=0.94 (3H, t, J=7.4 Hz), 1.47—1.79 (2H, m), 2.08 (3H, s), 2.72—2.90 (2H, m), 2.98—3.12 (1H, m), 7.41—7.57 (2H, m), 8.02—8.10 (2H, m); IR (neat) 1352, 1530, 1711 cm^{-1}; $[\alpha]_D^{20}$ +9.4 (*c* 1.04, $CHCl_3$). Found: C, 65.36; H, 6.97; N, 6.09%. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33%.

4-Aryl-3-methyl-3-buten-2-one-4-*d* (1a-*d* and 1e-*d*). To a stirred suspension of 1.0 g (23.8 mmol) of $LiAlD_4$ in 40 ml of dry THF, 40 mmol of methyl benzoate in 80 ml of dry THF was added dropwise under an atmosphere of argon. The reaction mixture was heated under reflux for 3 h. The cooled suspension was poured into ice-water. The organic layer was separated and washed with aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure to give an arylmethan-d_2-ol **5a**-d_2. (3,4-Dimethoxyphenyl)methan-d_2-ol (**5e**-d_2) was obtained similarly.

5a-d_2: 79% yield; ^{1}H NMR ($CHCl_3$) δ=1.75 (1H, s), 7.23—7.39 (5H, m); IR (neat) 2091, 3331 cm^{-1}.

5e-d_2: 64% yield; ^{1}H NMR ($CHCl_3$) δ=3.89 (3H, s), 3.90 (3H, s), and 6.83—6.95 (3H, m).

To a suspension of 10.8 g (50 mmol) of pyridinium chlorochromate (PCC) and 20 g of alumina in 60 ml of CH_2Cl_2, 20 mmol of **5**-d_2 was added and stirred for 2.5 h at room temperature. The mixture was chromatographed over a florisil column to give arenecarbaldehyde-*d* **6**-*d*.

6a-*d*: 29 yield; ^{1}H NMR ($CHCl_3$) δ=7.51—7.70 (3H, m), 7.87—7.91 (2H, m); IR (neat) 1688, 2052, 2106 cm^{-1}.

6e-*d*: 47% yield; ^{1}H NMR ($CHCl_3$) δ=3.96 (3H, s), 3.98 (3H, s), 6.99 (1H, d, *J*=8.0 Hz), 7.43 (1H, d, *J*=1.8 Hz), 7.48 (1H, dd, *J*=1.8, 8.0 Hz).

Butenones **1a**-*d* and **1e**-*d* were prepared from **6a**-*d* and **6e**-*d*, respectively, in the same manner as described above.

3-Methyl-4-phenyl-3-buten-2-one-4-*d* (1a-*d*): 55% yield; ^{1}H NMR ($CHCl_3$) δ=2.06 (3H, s), 2.47 (3H, s), 7.31—7.44 (5H, m); IR (neat) 1667, 2359 cm^{-1}.

4-(3,4-Dimethoxyphenyl)-3-methyl-3-buten-2-one-4-*d* (1e-*d*): 38% yield; ^{1}H NMR ($CHCl_3$) δ=2.10 (3H, s), 2.46 (3H, s), 3.92 (3H, s), 3.93 (3H, s), 6.92 (1H, d, *J*=8.2 Hz), 6.99 (1H, d, *J*=2.0 Hz), 7.08 (1H, dd, *J*=2.0, 8.2 Hz).

4-Aryl-3-ethyl-3-buten-2-one (7a and 7h). In a 200 mL flask, 71 mL of acetic acid, 8.7 g (100 mmol) of 2-pentanone, and 50 mmol of arenecarbaldehyde were placed. The solution was stirred at room temperature. To the solution, 7.4 g of H_2SO_4 was added slowly. After 12 h, the reaction mixture was added to 50 mL of water, neutralized with 20% aqueous NaOH, and extracted with ethyl acetate. The ethyl acetate solution was washed with aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel with hexane/ethyl acetate (10/1: v/v) as an eluent and recrystallization from ethanol to give 4-aryl-3-ethyl-3-buten-2-one.

3-Ethyl-4-phenyl-3-buten-2-one (7a): 43% yield; ^{1}H NMR ($CHCl_3$) δ=1.11 (3H, t, *J*=7.4 Hz), 2.45 (3H, s), 2.53 (2H, q, *J*=7.4 Hz), 7.37—7.42 (5H, m), and 7.48 (1H, s); IR (neat) 1667 cm^{-1}. Found: C, 82.62; H, 8.24%. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10%.

3-Ethyl-4-(3-nitrophenyl)-3-buten-2-one (7h): 52% yield; ^{1}H NMR ($CHCl_3$) δ=1.13 (3H, t, *J*=7.4 Hz), 2.48 (3H, s), 2.51 (2H, q, *J*=7.4 Hz), 7.46 (1H, s), 7.57—7.72 (2H, m), 8.19—8.26 (2H, m); IR (KBr) 1350, 1530, 1667 cm^{-1}. Found: C, 65.67; H, 5.91; N, 6.28%. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39%.

(*S*)-(+)-3-Ethyl-4-(3-nitrophenyl)-2-butanone (8h). In a 2 L flask, 250 g of raw bakers' yeast, 500 mL of water and 2.56 g of **7h** (11.7 mmol) were placed. The mixture was shaken for 3 d at 30 °C. To the reaction mixture, 1 L of acetone was added and the mixture was filtered. The precipitate was washed with 1 L of acetone and the washing solution was combined with the filtrate. The mixture was concentrated under reduced pressure to 200 mL and organic materials were extracted with ethyl acetate. The ethyl acetate solution was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel with hexane/ethyl acetate (10/1: v/v) as an eluent to obtain (*S*)-3-ethyl-4-(3-nitrophenyl)-2-butanone (**8h**) in 56% yield.

(*S*)-(+)-2-Ethyl-3-(3-nitrophenyl)propionic Acid (9). A slight modification of the reported method was adopted for the synthesis of this compound.[18] In a 50 mL round bottomed flask, 2.3 g of $Ca(OCl)_2$ (25 mmol) was suspended in 14 mL of water. A solution of KOH (0.7 g, 12.5 mmol) and K_2CO_3 (2.44 g, 17.7 mmol) in 7.0 mL of water was added. The flask was sealed by glass stopper and shaken until the initial gelatinous precipitate liquefied. The potassium hypochlorite solution (containing approximately 0.14 mol of KOCl) was then filtered to remove the precipitated calcium salts. The resulting solution was cooled to 0 °C, and 178 mg of **8h** (0.8 mmol) was added to the vigorously stirred solution by using a small amount of $CHCl_3$. The mixture was stirred vigorously overnight at room temperature. The reaction was quenched by adding 1 g of $NaHSO_3$ and the solution was acidified to pH 3 by the addition of 6 M HCl. (1 M=1 mol dm^{-3}). The aqueous solution was extracted with CH_2Cl_2 and the combined extracts were washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel with hexane/ethyl acetate (1/1: v/v) to give 80 mg of the substrate (45%) and 51.2 mg of (*S*)-2-ethyl-3-(3-nitrophenyl)-propionic acid (**9**) in 52% yield. ^{1}H NMR ($CHCl_3$) δ=1.00 (3H, t, *J*=7.6 Hz), 1.53—1.80 (2H, m), 2.60—2.73 (1H, m), 2.88 (1H, dd, *J*=6.1, 14.0 Hz), 3.07 (1H, dd, *J*=8.6, 14.0 Hz), 7.41—7.55 (2H, m), 8.06—8.12 (2H, m); IR (neat) 1352, 1530, 1707 cm^{-1}; $[\alpha]_D^{20}$ +34.4 (*c* 2.56, $CHCl_3$); lit,[19] *S*-form (92% ee): $[\alpha]_D^{25}$ +29.93 (*c* 0.742, $CHCl_3$). Found: C, 58.99; H, 6.04; N, 5.99%. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27%.

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