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Synthesis of Chiral 5-Aryltetrahydrofuran-2-ones via Yeast Bioreduction of γ-Keto Acids and Their Esters*

N. O. Mahmoodi and R. Yousefi-Malekroudi

Organic Research Laboratory, Department of Chemistry University of Guilan, Rasht, P.O.Box 1914, Iran
e-mail: mahmoodi@guilan.ac.ir

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Abstract—Enantioselective reduction of γ-keto acids and related γ-keto esters with *Saccharomyces cerevisiae* (baker's yeast) leads to the formation of the corresponding chiral 5-aryltetrahydrofuran-2-ones in satisfactory chemical and optical yields.

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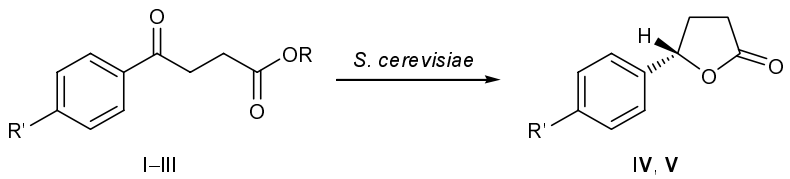
γ-Lactone ring is present in numerous optically active natural products isolated from plants, fungi, insects, and marine organisms [1–5]. Consequently, the synthesis of such heterocyclic subunits in enantiomerically pure form has attracted specific attention. Among several known synthetic approaches [6–8], enantioselective reduction of the corresponding γ-keto acids or their ester intermediates with the aid of enzymes (either isolated or as a whole cell system) is characterized by general applicability. Baker's yeast *Saccharomyces cerevisiae* is used most frequently as effective biocatalyst in asymmetric syntheses [9–12]. Yeast bioreduction with *Saccharomyces cervisiae* was applied to such dicarbonyl substrates as β-keto esters [13–18], α-keto esters [19], α-keto phosphates [20], and α-diketones [21], as well as to some ketones [22]. These reductions often showed a high degree of stereoselectivity. We recently reported on enantio-, regio-, and chemoselective reduction of some symmetric and asymmetric *para*-substituted benzyl derivatives with *S. cervisiae* under aerobic fermenting conditions (CO_2 evolution) in aqueous alcohol (phosphate buffer, pH 7, 0.01 M) [8].

In the present communication we report on the bioreduction of 4-oxo-4-phenylbutanoic acid (**I**) [23], its ethyl ester **II**, ethyl 4-(4-methoxyphenyl)-4-oxobutanoate (**III**), and ethyl 2-benzoylbenzoate (**VI**) with *Saccharomyces cerevisiae* with the goal of preparing the corresponding enantiomerically pure γ-lactones through intermediate γ-hydroxy derivatives (Schemes 1 and 2). The reduction was carried out according to modified procedure [8]. From compounds **I**–**III** we obtained chiral 5-aryltetrahydrofuran-2-ones **IV** and **V** in satisfactory chemical and optical yields.

Our attempts to synthesize lactone **VII** from ester **VI** [24] were unsuccessful even after optimization of the reaction conditions. As a result, we isolated the corresponding acid **VIII** and ethyl 2-(α-hydroxybenzyl)benzoate (**IX**) (Scheme 2). Obviously, aromatic γ-keto derivatives are considerably less reactive than their aliphatic analogs [25, 26]. The synthesis of optically inactive lactone **VII** from 2-benzoylbenzoic acid was described by us in [24].

We previously [23] tried to obtain racemic lactone **V** by cyclization of 4-(4-methoxyphenyl)butanoic acid in the system sodium peroxodisulfate–copper(II)

Scheme 1.

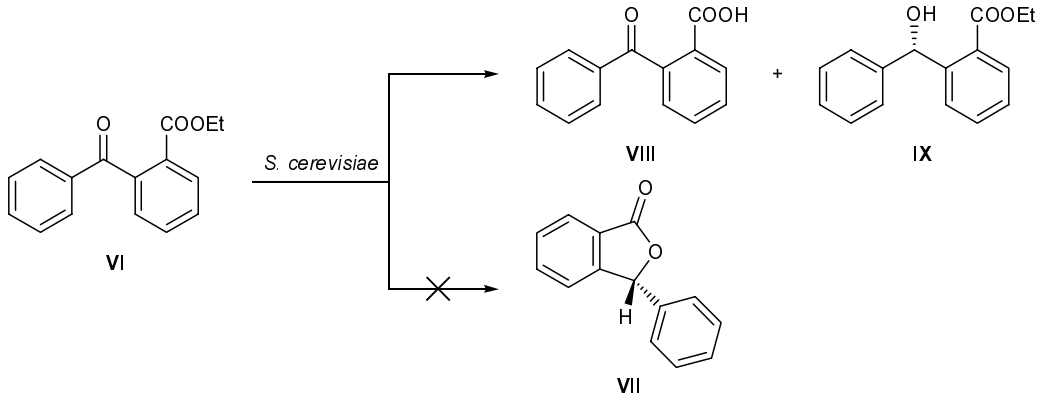


I–III IV, V

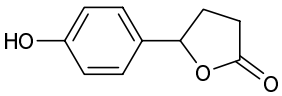
I, R = R' = H; **II**, R = Et, R' = H; **III**, R = Et, R' = MeO; **IV**, R' = H; **V**, R' = MeO.

* The text was submitted by the authors in English.

Scheme 2.



chloride. However, the reaction was accompanied by demethylation, and we isolated in high yield 5-(4-hydroxyphenyl)tetrahydrofuran-2-one (**X**) instead of expected lactone **V**. Enzymatic reduction of ester **III** in the presence of *S. cerevisiae* afforded optically active γ-lactone (–)-(**V**), the methoxy group in the aromatic ring being retained.



X

EXPERIMENTAL

Compounds **I**, **II**, and **VII** were synthesized as described in [23, 24] and were subjected to esterification in anhydrous ethanol. Most of the other chemicals were purchased from Fluka, Merck, and Aldrich. Commercial baker's yeast *S. cerevisiae* as active and dry material (Saf-levure, S.I.Lesaffre 59703, Mareq, France) was used. The reaction products were characterized by melting points, GLC and TLC data, and IR and NMR spectra, as well as by comparing with authentic samples (for previously reported compounds). The yields refer to compounds isolated by column or preparative thin-layer chromatography.

The melting points were determined on a Mettler Fp5 melting point apparatus. The specific rotations were measured on an ATAGO (POLAX) polarimeter (cell path lengths 5 and 10 cm). The IR spectra were recorded on a Shimadzu IR-470 spectrometer. The ^{1}H and ^{13}C NMR spectra were measured from solutions in $CDCl_3$ on a Bruker FT-500 instrument at 500 and 125 MHz, respectively; tetramethylsilane was used as internal reference.

(–)-(*S*)-5-Phenyltetrahydrofuran-2-one (IV). *a*. The reaction was carried out in a 500-ml three-necked flask equipped with a gas-outlet tube which was connected (through an intermediate bottle) to a 200-ml bottle filled with a saturated aqueous solution of $Ba(OH)_2$ (the end of the tube was placed below the solution surface). The flask was charged with 40 g (120 mmol) of sucrose, 400 ml of warm tap water, and 0.5 g of Na_2HPO_4, the mixture was stirred for several minutes at room temperature until it became homogeneous, and 40 g of active dry yeast was added. The mixture was stirred for 30 min at 30°C, and a solution of 0.19 g (1.07 mmol) of 4-oxo-4-phenylbutanoic acid (**I**) in 20 ml of 96% ethanol containing 1 ml of a 1 M solution of potassium hydroxide was added dropwise through a syringe over a period of 2 h. The mixture was vigorously stirred for 192 h at 30°C, the progress of the reaction being monitored by TLC (eluent ligroin–ethyl acetate, 2:1). Celite, 30 g, was added to remove the yeast, and the precipitate was filtered off and washed with water (2×25 ml). The filtrate was acidified to pH 2 and extracted with diethyl ether (5×20 ml). The extracts were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by preparative thin-layer chromatography (eluent ethyl acetate–ligroin, 1:2). Yield 0.03 g (15%), $[\alpha]_D^{25}$ = –32° (*c* = 0.44, $CHC1_3$), *ee* = 98.4% [27, 28]. IR spectrum (film), ν, cm^{-1}: 3010 w, 2990 m, 1770 s, 1450 m, 1250 m, 1020 m, 695 m. ^{1}H NMR spectrum, δ, ppm: 2.2 sept (COCH, *J* = 3.7 Hz), 2.7 d.d.t (COCHC**H**$_2$, *J* = 3.3. 3.3, 2.2 Hz), 5.7 t (COOCH, *J* = 7.3 Hz), 7.35 m (5H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 29, 31, 82, 125, 128, 129, 130, 164.

b. Compound **IV** was synthesized as described above in *a* from 0.22 g (1.07 mmol) of ethyl 4-oxo-4-phenylbutanoate (reaction time 168 h). The progress of the reaction was monitored by TLC (eluent ligroin–ethyl acetate, 10:3). The crude product, 0.2 g (90.1%),

was purified by preparative thin-layer chromatography (eluent ethyl acetate–ligroin, 3:10). Yield 0.056 g (33%), $[\alpha]_D^{25} = -32.5°$ ($c = 0.44$, $CHCl_3$), *ee* >99% [29], mp 34–36°C; published data [29]: mp 35–36°C. The IR and ^1H NMR spectra were identical to a sample prepared as described above in *a*.

Ethyl 4-(methoxyphenyl)-4-oxobutanoate (III). Concentrated sulfuric acid (98%), 4 ml, was carefully added dropwise under stirring to a mixture of 2.08 g (10 mmol) of 4-(methoxyphenyl)-4-oxobutanoic acid **XII** [23], 23 ml of anhydrous ethanol, and 32 ml of benzene (freshly distilled over metallic sodium). The mixture was stirred for 10 min at room temperature and was then heated under reflux over 14 h. The mixture was cooled to room temperature, 90 ml of water was added, the organic phase was separated, and the aqueous phase was extracted with diethyl ether (3×30 ml). The extracts were combined with the organic phase, washed with a saturated solution of $NaHCO_3$ (2×10 ml), dried over $MgSO_4$, filtered, and evaporated. The residue was a semisolid substance. Yield 1.84 g (79%), mp 33–35°C. IR spectrum (KBr), ν, cm^{-1}: 3000 m, 2980 m, 1705 s, 1680 s, 1400 m, 1240 s, 1180 m, 840 s. ^1H NMR spectrum, δ, ppm: 1.3 t ($CH_2C\mathbf{H}_3$, J = 7.1 Hz), 2.7 t ($OCOCH_2$, J = 6.7 Hz), 3.3 t ($COCH_2$, J = 6.7 Hz), 3.9 s (OCH_3), 4.2 q ($C\mathbf{H}_2CH_3$, J = 7.1 Hz), 6.9 d (2H, *m*-H, J = 3.7 Hz), 8.0 d (2H, *o*-H, J = 8.7 Hz).

Compounds **II** and **VI** were synthesized in a similar way.

Ethyl 4-oxo-4-phenylbutanoate (II) was synthesized from 1.78 g (10 mmol) of 4-oxo-4-phenylbutanoic acid (**I**) [23] and 20 ml of anhydrous ethanol in 30 ml of benzene (freshly distilled over sodium). Compound **I** was isolated as a white syrup. Yield 1.72 g (83%), mp 48–50°C. IR spectrum (KBr), ν, cm^{-1}: 3050 br, 2950 m, 1740 s, 1440 m, 1200 s, 1160 m, 750 s, 695 s. ^1H NMR spectrum, δ, ppm: 1.2 t ($CH_2C\mathbf{H}_3$, J = 7.1 Hz), 2.7 t ($OOCCH_2$, J = 6.6 Hz), 3.3 t ($COCH_2$, J = 6.6, 7.2 Hz), 4.1 q ($C\mathbf{H}_2CH_3$, J = 7.1 Hz), 7.4 t (2H, H_{arom}, J = 3.1, 7.2 Hz), 7.5 t (1H, H_{arom}, J = 7.4 Hz), 7.9 d (2H, H_{arom}, J = 13.0 Hz).

Ethyl 2-benzoylbenzoate (VI) was synthesized from 2.26 g (10 mmol) of 2-benzoylbenzoate (**VIII**) [24] and 27 ml of anhydrous ethanol in 30 ml of benzene (freshly distilled over metallic sodium). Yield 1.98 g (78%), colorless crystals, mp 53–55°C. IR spectrum (KBr), ν, cm^{-1}: 3050 m, 2980 m, 1720 s, 1680 s, 1580 m, 1440 m, 1230 m, 1080 m, 790 m. ^1H NMR spectrum, δ, ppm: 1.0 t ($CH_2C\mathbf{H}_3$, J = 7.1 Hz), 4.1 q ($C\mathbf{H}_2CH_3$, J = 7.1 Hz), 7.4 (3H, H_{arom}, J = 16 Hz), 7.5 t (2H, H_{arom}, J = 7.7, 9 Hz), 7.6 d.d (2H, H_{arom}, J = 0.76, 2.4 Hz), 7.8 t (1H, H_{arom}, J = 7.4 Hz), 8.1 d (1H, H_{arom}, J = 7.6 Hz).

(–)-5-(4-Methoxyphenyl)tetrahydrofuran-2-one (V) was synthesized as described above for compound **IV** from 0.25 g (1.06 mmol) of ethyl 4-(4-methoxyphenyl)-4-oxobutanoate (**III**) (reaction time 144 h; TLC, ethyl acetate–ligroin, 1:2.5). Yield of crude product 0.2 g (80%); after purification by preparative thin-layer chromatography (ethyl acetate–ligroin, 1:2.5), yield 0.12 g (59.5%), $[\alpha]_D^{25} = -35°$ (c = 0.76, $CHCl_3$); *ee* value and absolute configuration were not determined for the lack of the corresponding published data. IR spectrum (film), ν, cm^{-1}: 3050 m, 2980 m, 1760 s, 1450 m, 1240 m, 1190 m, 830 m. ^1H NMR spectrum, δ, ppm: 2.2 d.d ($CH_2C\mathbf{H}$, J = 8, 13 Hz), 2.6 d.d.d.d ($C\mathbf{H}_2CH$, J = 7.7, 6.6 Hz), 3.8 s (CH_3), 5.4 t (OCH, J = 8 Hz) 6.9 d (2H, H_{arom}, J = 8 Hz), 7.3 d (2H, H_{arom}, J = 8 Hz). ^{13}C NMR spectrum, δ_C, ppm: 29, 30, 56, 81, 126, 128, 130, 158, 176.

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