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Synthesis of optically active methyl 4-(4-biphenylyl)-3-hydroxybutanoate via enantioselective hydrogenation using a tartaric acid-modified nickel catalyst and recrystallization

Takashi Sugimura [a,*], Tomohiro Matsuda [a], Tsutomu Osawa [b]

[a] *Graduate School of Material Science, University of Hyogo, 3-2-1 Kohto, Kamigori, Ako-gun, Hyogo 678-1297, Japan*
[b] *Graduate School of Science and Engineering for Research, University of Toyama, Gofuku, Toyama 930-8555, Japan*

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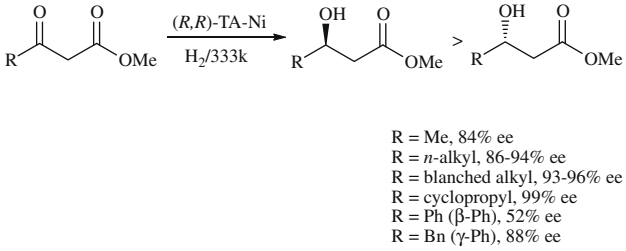
ABSTRACT

Enantioselective hydrogenation of methyl 4-(4-biphenylyl)-3-oxobutanoate over a tartaric acid-modified Raney nickel catalyst gave the title compound in 82% ee, which was enantiomerically enriched by recrystallizations. The product was converted to an (*R*)-3-acetoxyglutaric acid half ester via a ruthenium-catalyzed oxidation.

1. Introduction

4-Aryl-3-hydroxybutanoic acids are antiinflammatory compounds found through the UV erythema and rat paw tests with the extended analogues of mephenesin and chlorphenesin. Of the compounds tested, 4-(4-biphenylyl)-3-hydroxybutanoic acid and its esters have the highest activity, and show 2.5–5.6 times higher pharmacological activities than phenylbutazone, a common non-steroidal anti-inflammatory drug.[1] In addition, optically active 4-aryl-3-hydroxybutanoate esters can be precursors for 3-alkoxyglutaric acid half esters, key synthetic units for various natural and unnatural bioactive compounds.[2] Such optically active β-hydroxyesters are obtained by the enantioselective hydrogenation of the corresponding β-ketoesters using either homogeneous or heterogeneous chiral catalysts. Although the heterogeneous catalysts are more advantageous for practical large scale synthesis,[3] efficient enantioselectivity is more difficult to attain than with homogeneous catalysts.

A tartaric acid-modified nickel (TA-Ni) catalyst has been established for that purpose.[4] So far, the TA-Ni prepared from Raney nickel co-modified with NaBr has the highest catalytic activity, and gives a moderately high 84% ee on hydrogenation of methyl acetoacetate, a simple standard substrate, and a higher ee of 86–96% from γ-alkyl-substituted β-ketoesters (Scheme 1).[5] Although the highest ee has reached 99% with a specific substrate (R = cyclopropyl),[6] the ee values obtained with other substrates were not sufficiently high for starting materials for pharmaceutical products. Recrystallization of the hydrogenation products is a practical method to obtain purer enantiomers, but the products studied so far are not crystalline including those obtained from more than fifty alkyl-substituted β-ketoesters. An enantiomeric enrichment procedure consisting of hydrolysis of the product, salt formation with an amine, recrystallization, neutralization, and esterification is available for liquid ester products,[7] but a simpler and more effective procedure is still required.



Scheme 1. Stereoselectivity for the hydrogenation of β-ketoesters with (*R*,*R*)-TA-Ni.

Another limitation in the hydrogenation with TA-Ni is that β-ketoesters having an additional functional group, such as ether, ester, hydroxy, or amine, near the reaction site, at least at the α-, γ-, and δ-positions, are poor substrates and give lower product ee values.[8] Olefin, halide, and amide groups are also unsuitable because these groups themselves are reactive under the hydrogenation conditions. Effects of aryl groups are variable.[9] As given in Scheme 1, the β-phenyl substrate results in low ee of 52%, while γ-phenyl substitution gives 88% ee. Among the various β-aryl substrates studied so far, the higher ee values were obtained with the β-*p*-methoxyphenyl-β-ketoester (72%)[9] and β-3-(2,4-dimethylfuryl)-β-ketoester (90%),[10] but no additional data have been reported for analogues of the γ-phenyl substrate.

* Corresponding author. Tel.: +81 791 58 0168; fax: +81 791 58 0115.
E-mail address: sugimura@sci.u-hyogo.ac.jp (T. Sugimura).

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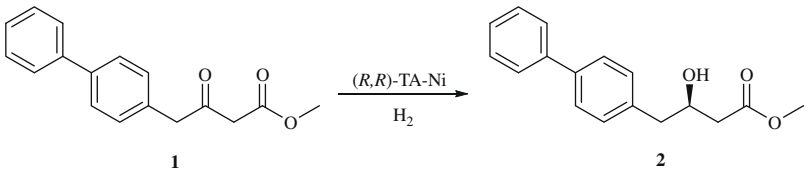


1 2

Scheme 2. Enantioselective hydrogenation of **1** over the tartaric acid-modified nickel (TA-Ni).

Herein, we would like to present results of the enantioselective hydrogenation with a γ-biphenylyl substrate, methyl 4-(4-biphenylyl)-3-oxobutanoate **1**, which provides the optically active anti-inflammatory compound **2** (Scheme 2). The product **2** was the first crystalline solid obtained from the TA-Ni-catalyzed hydrogenation, and the enantiomeric excess of **2** could be enriched by recrystallizations. Oxidation of **2** was also demonstrated to give optically active methyl hydrogen 3-acetoxyglutarate.

2. Results and discussion

When the hydrogenation of **1** was performed under the standard conditions,[6,13] in THF containing acetic acid (1%) under 9 MPa of hydrogen, the reaction was slow even at a low substrate/catalyst ratio (2–3 w/w), and so the concentration of the co-modifier (NaBr) was reduced to be half to make TA-Ni more active. The stereocontrollability of this catalyst was confirmed to be comparable with the standard TA-Ni by the hydrogenation of the γ-phenyl substrate (Scheme 1, R = Bn) at 333 K, which gave 88.1% ee as reported.[9] The hydrogenation of **1** was slower than that, while the reaction proceeded quantitatively to yield only **2** and the conversion after 24 h was more than 99% under the present hydrogenation conditions (Scheme 2). The ee values of the five repeated runs were in the range of 80.0–81.8%. When hydrogenation was carried out at a higher temperature of 373 K, the ee became lower at 75.6%. The absolute configuration of the product was estimated to be *R* from the stereocontrollability of the (*R*,*R*)-TA-Ni catalyst and the sign of the optical rotation (confirmed vide infra). The decrease in the ee by replacing γ-phenyl (88% ee) to γ-biphenylyl (82% ee) in the substrate was attributed to the increase in hydrophobicity at the γ-side by the extra phenyl group. Similar effects of hydrophobicity of the substituent remote from the reaction site were previously found with γ-alkyl-substituted β-ketoesters.[5,6]

After filtration and concentration of the hydrogenation mixture, **2** was obtained as colorless crystals. This is a very fortunate result because many γ-aromatic-β-hydroxybutanoate esters are not crystalline at least in their racemic forms.[1] We also prepared methyl 4-(1-naphthyl)-3-hydroxybutanoate and methyl 4-(3,4-dimethoxyphenyl)-3-hydroxybutanoate in the racemic forms, but they were not obtained as crystals. Recrystallization of the enantiomerically impure **2** was performed with toluene, diisopropyl ether, cyclopropyl methyl ether, and ethyl acetate as solvents. The efficiencies of the enantiomeric enrichment were similar in all solvents used, and the conditions were optimized with diisopropyl ether. From the reaction mixture of 80.0% ee, **2** of 95.7% ee was obtained in 57% yield by the three repeated recrystallizations.

Reasons for the exceptional crystallinity of **2** as a β-hydroxyester are examined by its crystallographic structure. In a crystal unit cell, the two biphenylyl-groups having a flat conformation are placed anti-parallel in the long axis and 70° tilted in the short axis relative to each other (Fig. 1a). Between the vicinal unit cells, the biphenylyl groups were arranged parallel to make a column, where the biphenylyls are tilted in 55° in the short axis. A notable structure is hydrogen bond chain with the 3-hydroxy group connecting vicinal columns (Fig. 1b). The distance of the hydrogen bond (2.71 Å) is a strain-free standard value indicating that the molecule is suitably packed in the crystal. As imagined from the crystallographic structure, racemic **2** gives conglomerate crystals, which was deduced from the comparison between the racemic and optically active **2** in their IR spectra and melting points.

The (3*R*)-**2** (>95% ee) obtained was converted to the acetoxy analogue **3** by conventional acetylation in 82% yield. The ruthenium-catalyzed oxidation of **3** with sodium periodate[14] gave the desired (3*R*)-methyl hydrogen 3-acetoxyglutarate **4** in 46% with a side product **5** in 5% yield (Scheme 3). Since oxidation of the benzoic acid derivative **5** is very slow under the present conditions, the ratio of **4**/**5** should indicate regioselectivity of the oxidation. The absolute configuration of **4** was determined to be *R* by the optical rotation,[12] and thus, the presumed stereochemistry of (3*R*)-**2** was confirmed.

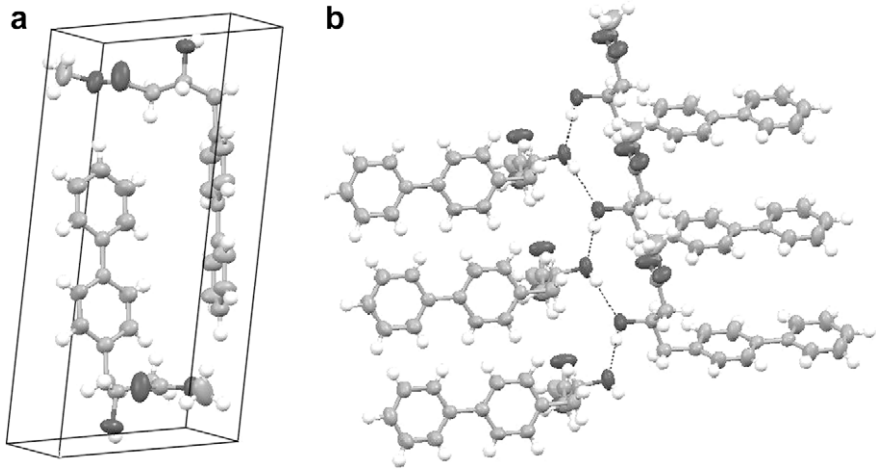
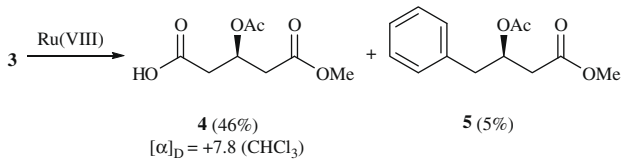


Figure 1. ORTEP diagrams for (3*R*)-**2**. Crystal data of $C_{17}H_{18}O_3$, *fw* = 270.33, monoclinic, $P2_1$, *a* = 7.8204(12), *b* = 5.5455(14), *c* = 16.8588(6) Å, α = 90°, β = 99.0582° (8), γ = 90°, *V* = 722.0(2) Å^3, *Z* = 2, D_{calcd} = 1.243 g cm^{-3}, $R(R_w)$ = 0.064(0.049) for 2807 reflections with $I > 2.0\sigma(I)$.



Scheme 3. Ruthenium-catalyzed oxidation to give (3*R*)-methyl hydrogen 3-acetoxyglutarate **4**.

3. Conclusions

The potent antiinflammatory agent **2** was prepared with moderately high enantioselectivity. Substituent effects to diminish the product ee were observed with the extra phenyl remote from the reaction site. The enantiomeric enrichment by recrystallization was demonstrated for the first time for the TA-Ni hydrogenation product. In addition, optically active **2** obtained by the present hydrogenation/recrystallization process was demonstrated to be a chiral synthon for desymmetrized 3-hydroxyglutaric acid analogues.

4. Experimental

4.1. Analysis

Melting points were determined using a Büchi B-545 melting point apparatus. NMR spectra were obtained by a JEOL ECA-600 spectrometer at 600 MHz for the proton spectra and 150 MHz for the carbon spectra, and by IR using a JASCO FT/IR-410 spectrometer. High resolution MS was obtained by a JEOL JMS-T100LC with electron spray ionization (ESI). Optical rotations were measured on a Perkin–Elmer-241 polarimeter. HPLC analysis was performed with Shimadzu LC-10AD and SPD-10A. The X-ray diffraction data were recorded using a Quantum CCD area detector on a Rigaku AFC-7R diffractometer at 295 K. CCDC deposition number 735401 contains the crystallographic data for this paper. These data can be obtained free of charge by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

4.2. Materials

The Raney nickel alloy with a ratio of Al/Ni = 58/42 was obtained from Kawaken Fine Chemicals Co., Ltd (Japan). Substrate **1** was prepared from 4-biphenylylacetic acid and Meldrum's acid (76% for two steps).[11] Mp 82.9–83.4 °C; ^{1}H NMR ($CDCl_3$) δ 7.53 (d, J = 7.8 Hz, 2H), 7.52 (d, J = 7.9 Hz, 2H), 7.39 (t, J = 7.9 Hz, 2H), 7.30 (t, J = 7.2 Hz, 1H), 7.22 (t, J = 11.0 Hz, 2H), 3.82 (s, 2H), 3.68 (s, 3H), 3.46 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 200.2, 167.5, 140.5, 140.3, 132.1, 129.9, 128.8, 127.5, 127.3, 127.0, 52.3, 46.6, 48.0; IR (KBr, cm^{-1}) 3031, 3005, 2957, 1749, 1439, 1311, 1260, 1213, 1133, 1014, 754, 696; HRMS (ESI+) m/z (M+Na$^+$) calcd for $C_{17}H_{16}NaO_3$ 291.0997, obsd 291.0994. THF and acetic acid were obtained from Wako Pure Chemical Industries, Ltd and used for the hydrogenation as obtained.

4.3. Hydrogenation

The Raney nickel alloy (1.9 g) was digested with a 20% NaOH solution at 373 K for 1 h. The catalyst was then washed with 500 mL of water (25 times of 20 mL). The activated Ni catalyst was immediately soaked in the preheated modification solution, which was obtained by dissolving (*R*,*R*)-TA (1.0 g) and NaBr (5.0 g) in water (100 mL), and adjusting at pH 3.2 with a 1 mol/L NaOH solution. The dispersion was kept at 373 K for 1 h, and decanted. The catalyst was then washed with water (one 10 mL portion), methanol (two 50 mL portions), and then THF (two 30 mL portions). The mixture of methyl 4-(4-biphenylyl)-3-oxobutanoate (1.5 g), THF (10 mL), and acetic acid (0.1 g) was subjected to the hydrogenation over the modified nickel catalyst. The initial hydrogen pressure was 9 MPa and the hydrogenation temperature was 333 K (or 373 K). The reaction mixture was filtrated after cooling, and analyzed by ^{1}H NMR to confirm the completion of the hydrogenation and by HPLC to determine the ee of the hydrogenation product **2**. Data for **2** (80% ee): Mp 101.3–102.7 °C; $[\alpha]_D^{20} = 14.6$ (c 1.0, methanol); ^{1}H NMR ($CDCl_3$) δ 7.52 (d, J = 7.2 Hz, 2H), 7.48 (d, J = 7.8 Hz, 2H), 7.37 (ddm, J = 7.2, 6.9 Hz, 2H), 7.28 (t, J = 6.9 Hz, 1H), 7.23 (d, J = 7.8 Hz, 2H), 4.25 (m, 1H), 3.64 (s, 3H), 2.97 (s, 1H, OH), 2.84 (dd, J = 13.2, 7.0 Hz, 1H), 2.75 (dd, J = 13.2, 6.0 Hz, 1H), 2.50 (dd, J = 15.6, 2.4 Hz, 1H), 2.43 (dd, J = 15.6, 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 173.0, 140.8, 139.5, 136.7, 129.8, 128.7, 127.2, 127.1, 126.9, 51.7, 42.5, 40.4; IR (KBr, cm^{-1}) 3401, 3038, 2947, 2924, 1730, 1486, 1436, 1408, 1197, 1160, 1064, 757, 687, 609; HRMS (ESI+) m/z (M+Na$^+$) calcd for $C_{17}H_{18}NaO_3$ 293.1154, obsd 293.1151.

Racemic **2** was also prepared by the sodium borohydride reduction of **1**. The spectral data were identical with optically active ones including IR spectrum (KBr), except for a broader melting point (92.0–94.2 °C). The HPLC analysis of **2** with a chiral column (Chiralpak AS-H, Daicel) resulted in a baseline separation (t_R = 19.67 for (*R*)-**2**, 24.98 min for (*S*)-**2**, eluted with a mixture of hexane/isopropanol = 95/5, 1 mL/min).

4.4. Enantiomeric enrichment

The hydrogenation product **2** (1.92 g, 80.0% ee) was dissolved in diisopropyl ether (80 mL) at 70 °C, and immediately kept in a refrigerator (−25 °C) overnight. Filtration gave 1.51 g of the crystalline **2** of 88.1% ee. The following second and third recrystallizations gave 1.30 g (92.1% ee) and 1.09 g (95.7% ee) of **2**, respectively. Total yield of the three recrystallizations was 57%. Mp 107.2–107.4 °C; $[\alpha]_D^{20} = +18.1$ (c 0.4, methanol).

4.5. Conversion of (*R*)-2 to (*R*)-3-acetoxyglutaric half ester

Optically active **2** was converted to the acetate analogue **3** as follows. A mixture of **2** (0.2 g), acetic anhydride (7.7 μL), pyridine (66 μL), and *N*,*N*-dimethylaminopyridine (4.5 mg) in THF (3 mL) was stirred for 1 h, and then extracted with ether (three times) to give crude **3** (229 mg), which was recrystallized in a mixture of hexane and ethyl acetate to give colorless powder (190 mg, 82%, mp 82.8–84.0 °C). To a solution of sodium periodate (19 g) in 35 mL of a solvent mixture of carbon tetrachloride/acetonitrile/water (2/2/3) was added **3** (0.5 g), followed by addition of ruthenium chloride hydrate (35 mg) at room temperature. After 5 days, the mixture was extracted with ether (six times), washed with water, dried over sodium sulfate, and concentrated to give the crude oxidized product (189 mg). The mixture was purified by a silica gel column (elution with 30% ethyl acetate in hexane, dichloromethane, and then methanol) to give **4** (150 mg, 46%), **5** (23 mg, 5%), and benzoic acid (27 mg, 14%). $[\alpha]_D^{20}$ of **4** = +7.8 (c 0.3, $CHCl_3$), lit. $[\alpha]_D^{20}$ for the (*R*)-isomer = +6.1 (c 20, $CHCl_3$).[12]

Acknowledgments

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