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New Technical Synthesis of Ethyl (*R*)-2-Hydroxy-4-phenylbutyrate of High Enantiomeric Purity

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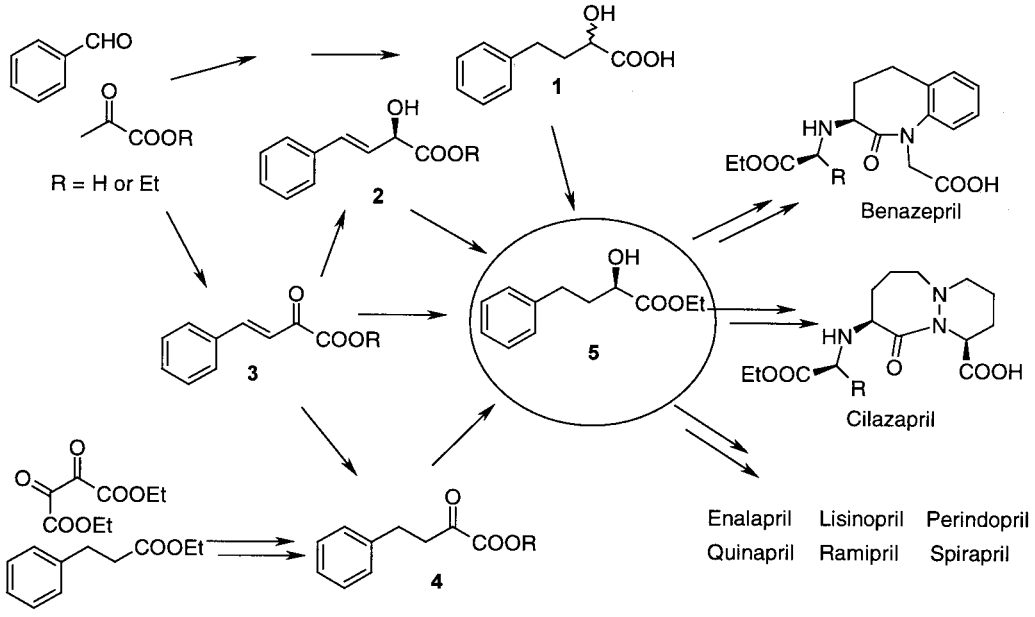
Abstract—A new technical synthesis to produce ethyl (*R*)-2-hydroxy-4-phenylbutyrate (**5**), an important intermediate for several ACE inhibitors with >99% ee in an over-all yield of 50–60% is described starting from acetophenone and diethyl oxalate. Key step is the chemo- and enantioselective hydrogenation of ethyl 2,4-dioxo-4-phenylbutyrate (**6**) (ee up to 86%) catalyzed by a heterogeneous Pt catalyst modified with dihydrocinchonidine, followed by crystallization of the 2-hydroxy-4-oxo ester **7** and hydrogenolysis of the 4-keto group.

A variety of commercially important Angiotensin-Converting Enzyme (ACE) inhibitors contain an (*S*)-homophenylalanine moiety which can be introduced starting from various building blocks.[1] One of the most useful is enantiomerically pure ethyl (*R*)-2-hydroxy-4-phenylbutyrate (**5**) which after introduction of a leaving group can be coupled with inversion with the respective amino moiety. Key transformations of existing technical processes to **5** are summarized in Scheme 1: (i) classical racemate resolution of the hydroxy acid **1**,[2] (ii) enantioselective reduction of the 3,4-unsaturated 2-keto acid **2** and esterification,[3,4] (iii) enantioselective reduction of the 2-keto acid **4** and esterification,[3,5] (iv) enantioselective hydrogenation or reduction of the 2-keto ester **4**.[3] However, all four routes have one or more weak points: (i) at best 50% yield, cost of pyruvic acid, (ii, iii) cost of pyruvic acid and difficulties with one or both



Scheme 1. Structures of ethyl (*R*)-2-hydroxy-4-phenylbutyrate (**5**), important intermediates and selected ACE inhibitors.

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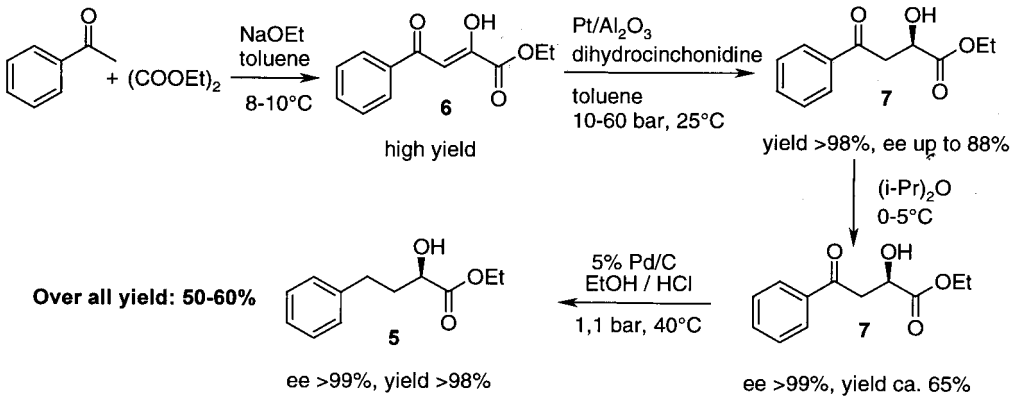

Scheme 2. New total synthesis of ethyl (*R*)-2-hydroxy-4-phenylbutyrate (**5**).

Table 1. Hydrogenation of ethyl 2,4-dioxo-phenylbutyrate (**6**): screening of catalyst and solvent

Entry	Catalyst	Type[a,b]	Modifier[c]	Solvent	ee (%)	Rate (mmol/g min)
1.1	5%Pt/Al_2O_3	JMC 94	HCd	Toluene	86	6.4
1.2	5%Pt/Al_2O_3	JMC 94	HCd	AcOH	45	3.6
1.3	5%Pt/Al_2O_3	JMC 94	HCd	EtOH	40	5.2
1.4	5%Pt/Al_2O_3	E 4759	HCd	Toluene	86	3.4
1.5	5%Pt/SiO_2	D TKS I	HCd	Toluene	60	6.8
1.6	5%Pt/SiO_2	D F340	HCd	Toluene	74	1.9

[a] Reaction conditions see Experimental (ee optimized procedure): 25°C, 60 bar.
[b] JMC Johnson Matthey, E Engelhard, D Degussa-Hüls.
[c] HCd: dihydrocinchonidine.

reduction steps (selectivity and/or catalyst activity), (iv) stability of keto ester (high purification losses), sensitivity of enantioselective hydrogenation to substrate quality.

Because many of these drugs either have lost patent protection or will soon do so, the cost of the required building blocks has become a major issue. Herein we describe a new cost efficient technical synthesis of **5** (ee>99%) with an over-all yield of 50–60%, starting from acetophenone and diethyl oxalate.[6]

For our re-engineering task we defined the following goals and prerequisites: (i) >99% chemical and enantiomeric purity; (ii) not more than four steps starting from low cost starting materials; (iii) enantioselective, high yield, preferentially catalytic transformations; (iv) easy purification. After assessing a variety of synthetic routes, we focused on the one depicted in Scheme 2: Claisen condensation, followed by chemo- and enantioselective hydrogenation of the resulting diketo ester **6**, and hydrogenolysis to **5**.

Claisen condensation[7] of acetophenone with diethyl oxalate proved to be straightforward. A quantitative yield of the 2,4-dioxo ester **6** was obtained by adding diethyl oxalate followed by acetophenone to a suspension of NaOEt in toluene, reacting at 8–10°C and work up (ice/acetic acid) and extraction.

The key step of the new synthesis was undoubtedly the chemo- and enantioselective hydrogenation of the 2,4-dioxo ester **6**. Based on our experience with the enantioselective hydrogenation of 2-keto acid derivatives, heterogeneous cinchona modified Pt catalysts were favored because both homogeneous and bio catalysts exhibited either too low activity or were difficult to scale up and/or to handle on a technical level.[3,8] However, the finding that the 2-keto group was fully enolized according to the NMR spectrum made predictions more difficult. With an extensive catalyst, modifier and solvent screening (for selected results see Table 1), followed by a careful parameter optimization we succeeded to develop a catalyst system that gave (*R*)-2-hydroxy-4-oxo ester **7** as a viscous oil with high chemical yield, up to 86% ee and a reasonable catalyst activity.[9] As already observed for the hydrogenation of 2-keto esters,[8] the quality of **6** was of special concern to get good ee's.

In order to reach the necessary enantiomeric purity of >99%, enrichment was obviously required. It turned out that the partially enriched 2-hydroxy-4-oxo ester **7** was well suited for this purpose. DSC experiments indicated a melting point between 20 and 40°C and a solvent screening

Table 2. Hydrogenolysis of ethyl (*R*)-2-hydroxy-4-oxo-phenylbutyrate (**7**)

5% Pd/C	Solvent	Acid	Conditions	5[a]
10% (w/w)	AcOH	–	r.t.; 1.1 bar; 11 h	–[b]
	EtOH	–	r.t.; 1.1 bar; 20 h	–[b]
5% (w/w)	EtOH	HCl	r.t.; 1.1 bar; 4 h	>95%
	Toluene	H_3PO_4	55°C; 4 bar; 21 h	–[b]
	EtOH	H_2SO_4	50°C; 21 bar; 1.25 h	Quant.
	Toluene/EtOH	H_2SO_4	50°C; 21 bar; 1.5 h	Quant.

[a] No racemization but traces of the hydroxy acid were observed.
[b] Ethyl (2*R*, 4*R/S*))-2,4-dihydroxy-buyrate and not identified side-products were formed.

program enabled us to find suitable crystallization conditions where **7** of >72% ee was enriched to >99% ee in one crystallization step with yields between 50 and 70%, depending on the starting ee.

It is well known that aromatic ketones can be hydrogenated to the corresponding hydrocarbons in the presence of Pd catalysts.[10] However, catalyst activity is often low requiring high catalyst loadings and/or acidic conditions. As shown in Table 2, reasonable reaction times and very high chemoselectivity for the removal of the 4-keto group in **7** were indeed only achieved in the presence of a strong acid. Based on these results and further optimization of catalyst type and reaction conditions, a technical process was established operating at 1.1 bar at 40°C with a reaction time of <6 h giving >98% **5** with >99% ee containing ca. 1% (*R*)-2-hydroxy acid.

In conclusion, the new route described above gives an efficient and cost effective access to **5** that is now developed further in collaboration with the Life Science Molecules group of Ciba Specialty Chemicals (Ciba LSM) in order to produce t/y quantities for commercialization.

Experimental

All reagents and solvents were purchased from Fluka and used as received. ^{1}H an ^{13}C NMR spectra were recorded in $CDCl_3$ using a Bruker dpx 400 Fourier transform NMR spectrometer and data reported using the chemical shift scale in units of ppm relative to $SiMe_4$. Mass Spec analysis was carried out on a MAT 212 Finnigan apparatus, with EI ionization. HPLC analysis was carried out on a HP 1100 apparatus. Ethyl 2,4-dioxo-phenylbutyrate was synthesized according to the literature.[11]

Hydrogenation of ethyl 2,4-dioxo-phenylbutyrate (6), ee optimized procedure. 2.0 g diketo ester **6** in 30 ml toluene were hydrogenated at 25°C and 60 bar hydrogen pressure in a 50 ml stainless steel autoclave in the presence of 50 mg 5% Pt/Al_2O_3 (pretreated for 2 h in H_2 at 400°C) and 5 mg 10,11-dihydrocinchonidine. After hydrogen uptake had stopped (ca. 160 min), the catalyst was filtered off and the solution was evaporated to dryness at reduced pressure. Yield of **7**: 1.97 g, 98%, product content >97% (NMR), ee 86% (hplc, OD–H, hexane/EtOH 98.5/1.5, flow 0.7 ml/min; retention time: (*S*)-enantiomer 46.0 min, (*R*)-enantiomer 49.6 min). MS M+: 222. ^{1}H NMR ($CDCl_3$): 7.95 (d, 2H), 7.60 (dd, 1H), 7.45 (dd, 2H), 4.65 (m, 1H), 4.25 (q, 2H), 3.30–3.60 (m, 3H), 1.30 (t, 3H). ^{13}C NMR ($CDCl_3$), 198, 174, 136, 134, 129, 128, 67, 62, 42, 14 ppm.

Hydrogenation of 6, volume yield optimized procedure. 80.0 g diketo ester **6** in 120 ml toluene were hydrogenated at 25°C and 58 bar hydrogen pressure in a 300 ml stainless steel autoclave in the presence of 2.00 g 5% Pt/Al_2O_3 (pretreated for 2 h in H_2 at 400°C) and 200 mg 10,11-dihydrocinchonidine. After hydrogen uptake had stopped (ca. 140 min), the catalyst was filtered off and the solution was evaporated to dryness at reduced pressure. Yield of **7**: 76.0 g, 94%, product content >97% (NMR), ee 76% (hplc).

Crystallization of ethyl (*R*)-2-hydroxy-4-oxo-phenylbutyrate (7). 74 g (0.332 mol) of the residue of the hydrogenation was dissolved in 220 ml diisopropyl ether. Seeding crystals of enantiomerically pure (*R*)-2-hydroxy-4-oxo ester **7** were added and the solution was slowly cooled to 5°C. Yield of (*R*)-2-hydroxy-4-oxo ester **7**: 47 g, 64%, product content >99%, ee 99% (hplc, for method see **6**), mp 36–38°C. The ^{1}H NMR and the ^{13}C NMR spectra were identical with the one described above. $[\alpha]_D^{25}=+11.5$ (c=10, EtOH).

Typical hydrogenolysis procedure of ethyl (*R*)-2-hydroxy-4-oxo-phenylbutyrate (7). 46 g crystallized (*R*)-2-hydroxy-4-oxo ester **7** (ee >99%) was hydrogenated in 170 ml ethanol at 20°C and 1.1 bar hydrogen pressure in a glass autoclave in the presence of 1.0 wt% of a 5% Pd/C (460 mg) catalyst and 5 wt% HCl. After hydrogen uptake had stopped (5–6 h), the catalyst was filtered off and the solvent was evaporated in vacuo. Yield of **5**: 42 g, 98%, product content >98% according to ^{1}H NMR (^{1}H NMR ($CDCl_3$): 7.15–7.35 (m, 5H), 4.15–4.25 (m, 3H), 2.70–2.90 (m, 3H), 2.05–2.20 (m, 2H), 1.90–2.00 (m, 2H), 1.30 (t, 3H), ee >99% (hplc, OD–H, hexane/ethanol/TFA=970/30/0.4):); byproduct: <0.1% (*R*)-2-hydroxy-4-phenylbutyric acid.

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