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Efficient Application of Lipase-Catalyzed Transesterification to the Resolution of γ-Hydroxy Ketones

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In the memory of Professor Giuseppe Bellucci

Abstract: (±)-*trans*-2-(Benzoylmethyl)-1-cyclohexanol **4**, a γ-hydroxy ketone (γ-HK) obtained from the $Sc(OTf)_3$-catalyzed addition reaction of lithium enolate **1** with cyclohexene oxide **2**, was very efficiently resolved into (+)-*(1S,2R)*-**4** and acetate (-)-*(1R,2S)*-**6** [ee >99% for both (+)-**4** and (-)-**6**] by supported lipase PS-catalyzed enantioselective transesterification. The enantioselective $Sc(OTf)_3$-catalyzed addition of enolate **1** to propene oxide (+)-*(R)*-**3** and (-)-*(S)*-**3** is also described.

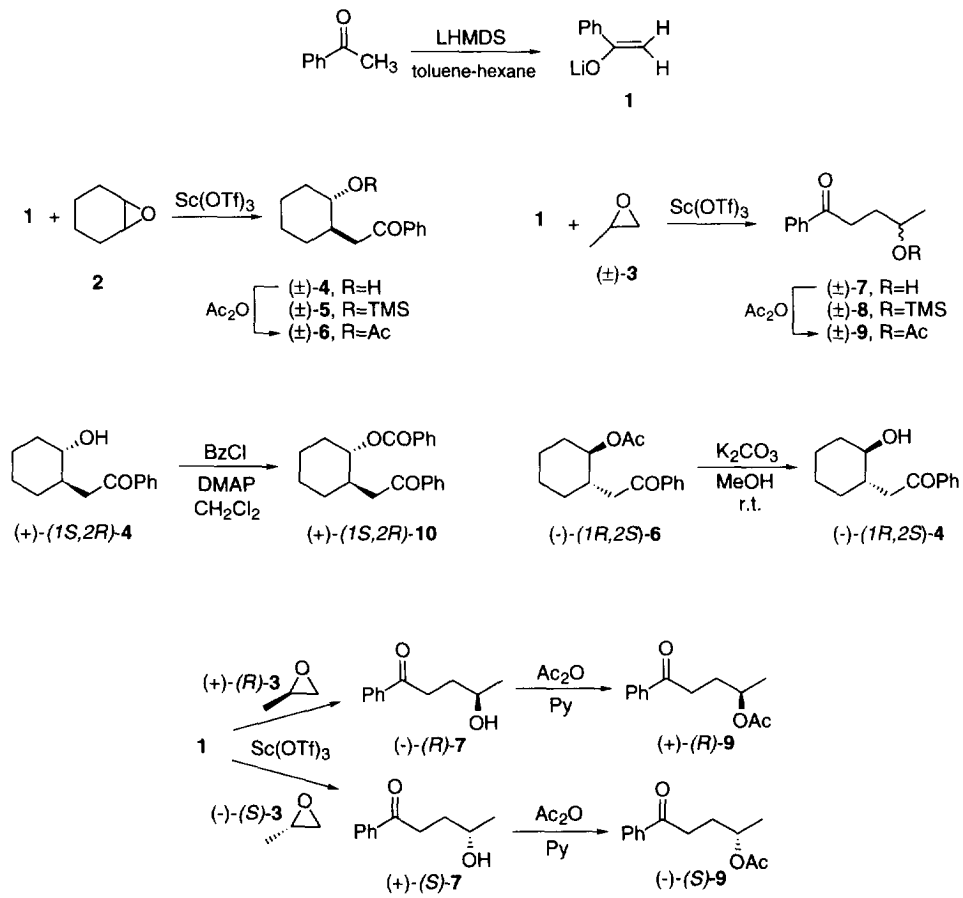
γ-Hydroxy ketones (γ-HKs)[1] constitute a simple difunctionalized system which, besides being of interest by itself, can be profitably utilized as a building block for the construction of more complex structures, such as polysubstituted tetrahydrofurans and other important heterocycles.[2] Even if the nucleophilic opening of a 1,2-epoxide with a metal enolate of a simple ketone is the most direct approach to the construction of the γ-HK moiety, this reaction has been taken into appropriate consideration only recently.[3,4] We reported that $Y(OTf)_3$ effectively catalyzes the addition of the lithium enolates derived from acetophenone **1** and pinacolone to some representative 1,2-epoxides, to give the corresponding γ-HKs in good yield.[3] This procedure appeared to be decidedly superior to the initially found $LiClO_4$-promoted one,[4] thus making the addition of lithium enolates of ketones (such as **1**, Scheme) to 1,2-epoxides a reaction of considerable synthetic interest. However, bicyclic 1,2-epoxides, such as cyclohexene oxide **2** still turned out, even in these $Y(OTf)_3$-catalyzed conditions,[3] to be somewhat less prone to addition. For this reason, many other catalysts were tested for the same reaction, and we found that $Sc(OTf)_3$, besides being very effective with typical aliphatic 1,2-epoxides, efficiently catalyzes the addition reaction of enolate **1** to bicyclic epoxide **2**.[5a]

In view of the growing general interest in enantiopure compounds and the possibility of the introduction of enantiopure γ-HKs, or some simple derivatives of these, into the chiral pool, as useful enantiopure building blocks, we examined various synthetic procedures which might allow the preparation of chiral γ-HKs with satisfactory ees. These procedures essentially include: *i)* the use of a chiral catalyst, *ii)* the use of appropriate chiral enolates or epoxides, and *iii)* the kinetic resolution of racemic γ-HKs. We now wish to report the results obtained in the kinetic resolution of two representative racemic γ-HKs, the (±)-*trans*-2-(benzoylmethyl)-1-cyclohexanol **4** and the aliphatic (±)-4-hydroxy-1-phenyl-1-pentanone **7**, by means of a lipase-catalyzed transesterification procedure (point *iii*). The addition of enolate **1** to enantiopure epoxides

(+)-*(R)*-**3** and (-)-*(S)*-**3** was also experimented (point *ii*).[5b]

The racemic (±)-**4** and (±)-**7** γ-HKs were prepared by reaction of the lithium enolate **1** with epoxides **2** and (±)-**3**, respectively, following a previously described procedure,[3] with the only difference being the use of $Sc(OTf)_3$ (10% equiv.) as the necessary metal salt catalyst.[5a] The same protocol was used also when the homochiral epoxides (+)-*(R)*-**3** and (-)-*(S)*-**3** were used as the electrophiles to give almost pure (-)-*(R)*-**7** (ee 96%) and (+)-*(S)*-**7** (ee 98%), respectively. In these reactions, the free OH γ-HKs **4** and **7** or the *O*-TMS protected ones **5** and **8** could be obtained depending on the work-up procedure, acid or non-acid, respectively (Scheme).[6]

Scheme

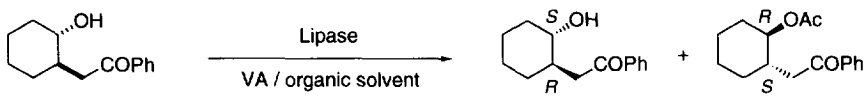


The (+)-*(1S,2R)*-**4** alcohol was transformed into its corresponding *O*-benzoyl derivative (+)-*(1S,2R)*-**10** (see below) by reaction with benzoyl chloride in anhydrous CH_2Cl_2, following standard procedures.

The racemic γ-HKs (±)-**4** and (±)-**7** were submitted to kinetic resolution by means of lipase-catalyzed enantioselective acylation in an organic solvent. The results obtained with a series of different types of

lipases, together with the experimental conditions, are shown in Tables 1 and 2. In every case, vinyl acetate (VA) was used as the acetylating agent, because of its proven ability to promote an irreversible reaction.[7]

Table 1. Lipase-Catalyzed Transesterification of (±)-*trans*-2-(Benzoylmethyl)-1-cyclohexanol **4**.



(±)-**4** (+)-*(1S,2R)*-**4** (-)-*(1R,2S)*-**6**

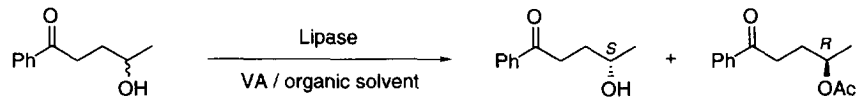
						(+)-*(1S,2R)*-**4**[d]		(-)-*(1R,2S)*-**6**	
Entry	Lipase (mg/mmol)	Solvent[a] (ml/mmol)	Temp (°C)	Time (h)	Conversion Ratio (**4**:**6**)[b]	Isolated Yield (%)[c]	ee (%)[e]	Isolated Yield (%)[c]	ee (%)[e]
1	PS supp. (1000)	VA/THF (7:3) (25)	37	3	50:50	96	>99	88	>99
2	PS supp. (1000)	VA/Hex (7:3) (25)	37	3	48:52	92	>99	75	>99
3	PS supp. (1000)	VA/THF (7:3) (25)	37	6	49:51	-	-	-	-
4	CCL (750)	VA/Hex (1:2) (15)	37	5	86:14	95	12	83	94
5	PPL supp. (1500)	VA (25)	37	72	83:17	98	17	90	>99
6	AY30 supp. (2150)	TBME[f] (25)	38.5	24	66:34	87	44	92	96
7	AK[g] (45)	TBME[h] (10)	38.5	6	56:44	95	69	89	>99

[a] VA = vinyl acetate; Hex = hexane; TBME = *t*-butyl methyl ether. [b] Determined by GC and ^{1}H NMR analysis. [c] Yields are corrected for the extent of substrate conversion. [d] The absolute configuration was determined by CD (see text). [e] ee Values were determined by chiral HPLC (for **4**) or GC (for **6**)(see Experimental Section). [f] 10 eq of VA was added. [g] For the experimental procedure, see ref. 12. [h] 20 eq of VA was added.

The best results were obtained with the cyclohexane system (±)-**4**, by means of a lipase PS supported on Hyflo Super Cell (entries 1 and 2, Table 1).[8] In this system the lipase PS was extremely selective towards the (-)-*(1R,2S)*-**4** enantiomer, and after 50% of conversion, both the acetate (-)-*(1R,2S)*-**6** and the recovered unreacted γ-HK (+)-*(1S,2R)*-**4**, which were easily separated by flash chromatography, turned out to be enantiomerically pure (ee >99%, Table 1). Subsequent saponification of acetate (-)-**6** with K_2CO_3 in MeOH at r.t. afforded enantiopure (-)-*(1R,2S)*-**4** (ee >99%), thus completing the resolution process of racemic (±)-**4**. The high enantioselectivity observed for both the acetate (-)-**6** obtained and the γ-HK (+)-**4** recovered in the transesterification reaction of (±)-**4** with lipase PS points to a large difference between the kinetic reaction constants of the two competing acetylation processes of the enantiomers of γ-HK **4**, so much so that the acetylation reaction essentially stops as soon as the (-)-*(1R,2S)*-**4** enantiomer has reacted.[8] This was demonstrated by the fact that reaction times (6 h) decidedly longer than the time (3 h) required for an almost

perfect 50% conversion (entries 1 and 2, Table 1) did not result in any significant modification of the conversion ratio between the unreacted γ-HK (+)-*(1S,2R)*-**4** and the acetate (-)-*(1R,2S)*-**6** (entry 3, Table 1).

Table 2. Lipase-Catalyzed Transesterification of (±)-4-Hydroxy-1-phenyl-1-pentanone **7**.



(±)-**7** (+)-*(S)*-**7** (+)-*(R)*-**9**

Entry	Lipase (mg/mmol)	Solvent[a] (ml/mmol)	Temp (°C)	Time (h)	Conversion Ratio (**7**:**9**)[b]	Isolated Yield (%)[c]	ee (%) of **9**[d]	Abs. Config. of **9**[e]
1	CCL (450)	VA/Hex (1:2) (10)	37	4.5	59:41	77	24	R
2	PPL[f] (400)	VA (15)	29	3	87:13	95	6	R
3	PPL[f] (400)	VA/TBME (7:3) (20)	30	6.5	66:34	71	8	R
4	PPL supp. (1000)	VA (20)	30	5	90:10	83	5	R
5	PS (350)	VA (20)	30	4	46:54	75	31	R
6	PS supp. (500)	VA (20)	30	4	9:91	69	25	R
7	PLE[g] (830)[i]	buffer[h] (60)	30	6	92:8	71	40	R
8	PS supp. (500)	*t*-AmOH[j,k] (20)	40	1.5	40:60	86	22	R
9	PS supp. (500)	VA/Pentane (7:3) (20)	40	1.5	32:68	93	30	R
10	PS supp. (500)	VA/THF (7:3) (20)	40	2	65:35	46	42	R
11	AK[l] (45)	TBME[m] (10)	35	5	58:42	87	13	S

[a-c] See corresponding footnotes in Table 1. [d] ee Values were determined by chiral HPLC. [e] Absolute configuration was determined by correlation with independently prepared enantiopure (+)-*(R)*- and (-)-*(S)*-**9**. [f] The enzyme was dried over P_2O_5 to constant weight. [g] PLE is an esterase; in this case the reverse reaction is involved, starting from the racemic acetate (±)-**9**. [h] Phosphate buffer (pH 8.0) / acetone (10%). [i] Value expressed in U/mmol. [j] *t*-AmOH = *t*-amyl alcohol. [k] 10 eq of VA was added. [l] For the experimental procedure, see ref. 12. [m] 50 eq of VA was added.

This particular behaviour of the racemic γ-HK (±)-**4** makes the resolution process in this system decidedly easy and practical.[8] The type and, in particular, the polarity of the organic solvent used does not seem to influence the enantioselectivity, since comparable ee values were obtained carrying out the reaction

in THF or hexane (entries 1 and 2, Table 1). When lipases different from lipase PS were used (Table 1, entries 4-7), the ee values of the reaction product, the acetate (-)-*(1R,2S)*-**6**, were still very high (94-99%), whereas the recovered unreacted γ-HK (+)-*(1S,2R)*-**4** showed a decidedly unsatisfactory degree of enantioselectivity (ee 12-69%). The chemical yields of isolated products were good in all cases.

With the aliphatic γ-HK system (±)-**7**, the corresponding enzymatic resolutions were not so successful as with the conformationally semirigid substrate (±)-**4** (Table 2). In spite of many modifications introduced by changing both the enzyme and the reaction conditions, the ee values of the acetylated product **9** were not superior to 42%, the best result being obtained, also in this case, with lipase PS supported on Hyflo Super Cell.[8] It is worth noting the interesting behaviour of lipase AK (entry 11, Table 2), which mainly gave the acetate (-)-*(S)*-**9**, while all the other lipases used gave the acetate (+)-*(R)*-**9** as the major enantiomer (entries 1-10, Table 2).

In conclusion, supported PS lipase gave impressive results in the kinetic resolution of the γ-HK (±)-**4** derived from the cyclohexene oxide **2**. Unfortunately, the same procedure was scarcely effective with the aliphatic γ-HK (±)-**7** derived from the propene oxide **3**. This unexpectedly large difference in the chemical behaviour towards the lipase-catalyzed acetylation process could reasonably be attributed to the consistently different conformational situation in the two systems, the semirigid (±)-**4** and the decidedly more mobile (±)-**7**, which shows up the discriminatory ability (enantioselectivity) of the enzyme.

The absolute configuration of γ-HK (+)-**4** (entries 1 and 2, Table 1), was determined by the CD method carried out on the corresponding benzoyl derivative (+)-**10** (Scheme and Figure).

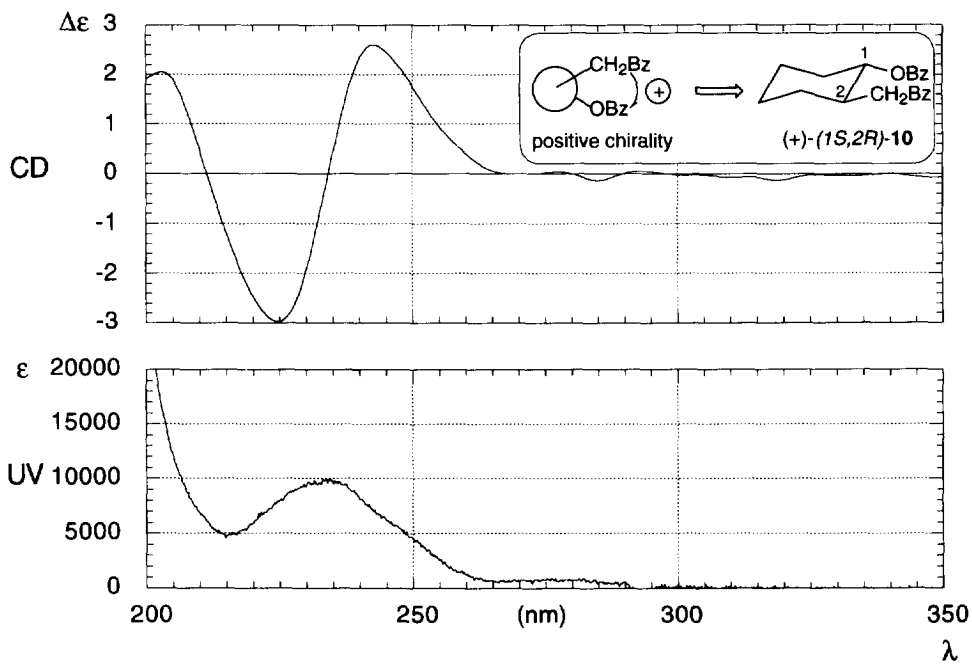


Figure. CD and UV Spectra of (+)-*(1S,2R)*-2-(Benzoylmethyl)-1-(benzoyloxy)cyclohexane **10**.

The presence in (+)-**10** of two similar chromophores (the PhCO- keto group and the PhCOO- ester group) located in stereogenic positions with respect to each other and exhibiting a strong $\pi \rightarrow \pi^*$ transition absorption at approximately the same wavelength (230 and 240 nm, respectively) would have made it possible to observe an exciton couplet between the two chromophores and, as a consequence, to apply the Harada-Nakanishi rule.[9]

The CD spectrum of (+)-**10** (Figure) showed a clean positive couplet, with a maximum at 243 nm ($\Delta\epsilon$ = +2.6), a minimum at 225 nm ($\Delta\epsilon$ = -3.0), and, correctly, with the crossing point on the λ axis (234 nm), corresponding to strongest UV absorption (λ_{max} = 234 nm, ϵ = 10000). As a consequence, the above CD pattern indicates for (+)-**10** a "positive chirality" between the two chromophores. Bearing in mind that in (+)-**4** the relationship between the two substituents on the cyclohexane ring is necessarily trans, in accordance with the commonly observed completely anti stereoselective ring opening process of typical aliphatic and cycloaliphatic oxirane systems under the reaction conditions used,[10] and that in the (+)-**4**→(+)-**10** transformation no stereogenic centre is involved, these results unequivocally assign the *(S)* configuration to carbon 1 (bearing the benzoyloxy group) and the *(R)* one to carbon 2 (bearing the benzoylmethyl group) of (+)-**10** (Figure). The same absolute configuration *(1S,2R)* necessarily has to be given to the starting γ-HK (+)-**4**.

The absolute configurations of γ-HK (+)-**7** and (-)-**7** were assigned by correlation (HPLC on chiral column) with the pure enantiomers independently prepared by the reaction of enolate **1** with pure (-)-*(S)*-**3** and (+)-*(R)*-**3** propene oxide, respectively (Scheme). In these conditions, where the nucleophilic attack occurs entirely on the less substituted oxirane carbon,[3] the configurations of the optically active γ-HKs (-)-*(R)*-**7** and (+)-*(S)*-**7** obtained were logically linked to those of the corresponding starting epoxides, (+)-*(R)*-**3** and (-)-*(S)*-**3**, respectively. The γ-HKs (-)-*(R)*-**7** and (+)-*(S)*-**7** were then transformed, by acetylation, into the corresponding (+)-*(R)*-**9** and (-)-*(S)*-**9** acetates which were used as standards in the HPLC analysis of the crude lipase-catalyzed transesterification of racemic (±)-**7**.

Experimental Section

Melting points were determined on a Kofler apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were determined with a Bruker AC-200 spectrometer on $CDCl_3$ solutions using tetramethylsilane as the internal standard. Optical rotations were measured with a Perkin-Elmer 241 digital polarimeter with a 1 dm cell. UV and CD spectra of compound (+)-**10** were recorded on a Varian CARY 2200 spectrophotometer and JASCO J600 spectropolarimeter, respectively. The enzymatic transesterification of (±)-**4** and (±)-**7** was followed by GC (FI detector) on a SE 52 glass column: column 170°C, injector and detector 250°C; nitrogen flow 20 ml/min. Racemic γ-HK **7** was prepared as previously described.[3] ee Values of γ-HKs (+)-*(1S,2R)*-**4** and (-)-*(1R,2S)*-**4** and acetates (+)-*(R)*-**9** and (-)-*(S)*-**9** were determined by HPLC on a Chiracel OD-H chiral column [25 cm x 0.46 cm (i.d.)] using a 92:8 and a 98:2 mixture of hexane and isopropyl alcohol, respectively: (+)-*(1S,2R)*-**4** and (+)-*(R)*-**9** were the first eluting enantiomers in each case. ee Values of acetate (-)-*(1R,2S)*-**6** were determined by GC (FI detector) on a Megadex 1 chiral capillary column [25 m x 0.32 mm (i.d.), 0.25 μm (film thickness)]: column temperature from 150°C to 190°C, ramp rate 1.5°C/min, injector 250°C, detector 300°C; nitrogen flow 0.8 ml/min. All reactions were followed by TLC on Alugram

SIL G/UV_{254} silica gel sheets (Macherey-Nagel) with detection by UV. Silica gel 60 (Macherey-Nagel 230-400 mesh) was used for flash chromatography. Toluene, THF and hexane were distilled from sodium/benzophenone ketyl under nitrogen atmosphere immediately prior to use. Benzoyl chloride and vinyl acetate (VA) were freshly distilled before use. *t*-Butyl methyl ether (TBME) was distilled from CaH_2 and stored over 4Å molecular sieves.

Enzymatic Materials.

Lipase PS (from *Pseudomonas sp.*), lipase AK (from *Pseudomonas sp.*), and lipase AY 30 (from *Candida rugosa*) were kindly provided by Amano Pharmaceutical Co. LTD, lipase CCL type VII (from *Candida cylindracea*) and lipase PLE (Pig Liver Esterase) were purchased from Aldrich, and lipase PPL type II crude (from porcine pancreas) was purchased from Sigma.

Lipase PS and AY 30 were immobilized onto Hyflo Super Cell following the procedure reported by Bovara.[8] Lipase PPL were supported on Hyflo Super Cell following the procedure described by Guanti.[11]

(±)-*trans*-2-(Benzoylmethyl)-1-cyclohexanol (4) and *O*-Trimethylsilyl Derivative 5.

A 1.0 M LHMDS solution in hexane (6.0 ml) was treated under stirring at 0°C with a solution of acetophenone (0.60 g, 5.0 mmol) in anhydrous toluene (1.0 ml), added over a period of about 10 min. After 15 min. at the same temperature, a solution of **2** (0.196 g, 2.0 mmol) in anhydrous toluene (2.0 ml) and $Sc(OTf)_3$ (0.098 g, 0.2 mmol) was added. The reaction mixture was allowed to warm slowly to r.t., stirred for additional 36 h, and then quenched with saturated aqueous NH_4Cl. Extraction with ether and evaporation of the washed (5% aqueous HCl and brine) ether extracts afforded a crude liquid (0.82 g) which was purified by flash chromatography (a 7:3 mixture of hexane and AcOEt was used as the eluant) to give pure **4** (0.370 g, 85% yield).[4]

When, in a similar reaction, the washing with 5% aqueous HCl was omitted, the crude liquid product (0.980 g) was subjected to flash chromatography (a 9:1 mixture of hexane and AcOEt was used as the eluant) to yield pure **(±)-*trans*-2-(benzoylmethyl)-1-(trimethylsilyloxy)cyclohexane 5** (0.40 g, 68% yield), as a liquid: ^1H NMR δ 7.94-7.99 (m, 2H), 7.39-7.53 (m, 3H), 3.49 (dd, 1H, *J*=14.9 and 3.4 Hz), 3.25-3.37 (m, 1H), 2.44 (dd, 1H, *J*=14.9 and 9.4 Hz), 1.56-2.03 (m, 5H), 1.17-1.47 (m, 3H), 0.12 (s, 9H); ^{13}C NMR δ 201.00, 137.32, 129.07, 128.87, 75.99, 43.16, 42.99, 36.57, 31.64, 30.25, 29.92, 25.95, 25.60, 0.88. Anal.Calcd for $C_{17}H_{26}O_2Si$: C, 70.34; H, 8.95. Found: C, 70.45; H, 8.74.

(±)-*trans*-2-(Benzoylmethyl)-1-(acetoxy)cyclohexane 6.

A solution of γ-HK (±)-**4** (0.050 g, 0.23 mmol) in anhydrous pyridine (2.0 ml) was treated at 0°C with Ac_2O (1 ml) and the reaction mixture was left at r.t. overnight. Dilution with water, extraction with ether and evaporation of the washed (5% aqueous HCl, saturated aqueous $NaHCO_3$ and brine) organic solution afforded pure (±)-**6** (0.056 g, 94% yield):^1H NMR δ 7.97-7.92 (m, 2H), 7.60-7.42 (m, 3H), 4.64-4.51 (m. 1H), 3.11 (dd, 1H, *J*=15.9 and 4.8 Hz), 2.67 (dd, 1H, *J*=15.9 and 7.9 Hz), 2.37-2.18 (m, 1H), 2.08-1.62 (m, 5H), 1.88 (s, 3H), 1.42-1.09 (m, 3H); ^{13}C NMR δ 200.03, 171.39, 137.77, 133.61, 129.22, 128.72, 77.47, 42.40, 39.71, 32.47, 32.21, 25.72, 25.14, 21.71. Anal.Calcd for $C_{16}H_{20}O_3$: C, 73.86; H, 7.68. Found: C, 74.05; H, 7.44.

(-)-*(R)*- and (+)-*(S)*-4-Hydroxy-1-phenyl-1-pentanone 7 and Corresponding *O*-(Trimethylsilyl) Derivatives 8.

Following the same procedure as described above for the preparation of γ-HK (±)-**4**, treatment of a solution of enolate **1** [from 1.0 M LHMDS in hexane (6.0 ml) and acetophenone (0.60 g, 5.0 mmol) in anhydrous toluene (1.0 ml)] with a solution of (+)-*(R)*-**3** (Fluka) (0.120 g, 2.0 mmol) in anhydrous toluene (2.0 ml) in the presence of $Sc(OTf)_3$ (0.098 g, 0.2 mmol) afforded a crude liquid reaction product (0.750 g) which was purified by flash chromatography (a 7:3 mixture of hexane and AcOEt was used as the eluant) to yield (-)-*(R)*-**7** (0.336 g, 94% yield):[4] $[\alpha]_D^{20}$= -12.08 (*c* 1.20, $CHCl_3$) (ee 96% determined on the corresponding acetate).

When the 5% aqueous HCl washing was omitted from the work-up procedure, the crude reaction product was subjected to flash chromatography (a 9:1 mixture of hexane and AcOEt was used as the eluant) affording pure ***(R)*-1-phenyl-4-(trimethylsilyloxy)-1-pentanone 8** (0.376 g, 75% yield), as a liquid: ^{1}H NMR δ 7.93-7.98 (m, 2H), 7.40-7.58 (m, 3H), 3.87-3.96 (m, 1H), 3.03 (dt, 2H, *J*=6.5 and 3.0 Hz), 1.72-1.93 (m, 2H), 1.20 (d, 3H, *J*=6.2 Hz), 0.09 (s, 9H); ^{13}C NMR δ 201.00, 137.71, 133.58, 129.23, 128.70, 68.28, 35.35, 34.17, 24.59, 0.89. Anal.Calcd for $C_{14}H_{22}O_2Si$: C, 67.19; H, 8.79. Found: C, 67.37; H, 8.53.

Following a similar procedure, when (-)*(S)*-**3** (Fluka) was used in the addition reaction with enolate **1**, the γ-HK(+)-*(S)*-**7** [0.32 g, 90% yield, $[\alpha]_D^{20}$=+12.04 (*c* 1.44, $CHCl_3$) (ee 98%)],[3] or the corresponding *O*-trimethylsilyl derivative*(S)*-**8** were obtained, depending on the work-up procedure (see above).

(+)-*(R)*-4-(Acetoxy)-1-phenyl-1-pentanone 9.

Following the same procedure as described above for the preparation of (±)-**6**, treatment of a solution of (-)-*(R)*-**7** (0.050 g, 0.28 mmol) in anhydrous pyridine (2.0 ml) with Ac_2O (0.5 ml) afforded pure (+)-*(R)*-**9** (0.049 g, 79% yield), as a solid, m.p. 33-35°C, $[\alpha]_D^{20}$= +3.58(*c* 0.83, $CHCl_3$): ^{1}H NMR δ 7.87-7.92 (m, 2H), 7.35-7.55 (m, 3H), 4.84 (m, 1H), 2.96 (dt, 2H, *J*=7.4 and 1.7 Hz), 1.96 (s, 3H), 1.90-2.05 (m, 2H), 1.22 (d,3H, *J*=6.2 Hz); ^{13}C NMR δ 199.9, 171.40, 137.44, 133.73, 129.25, 128.64, 71.08, 35.12, 30.83, 21.95, 20.78. Anal.Calcd for $C_{13}H_{16}O_3$: C, 70.92; H, 7.26. Found: C, 71.15; H, 7.49.

(-)-*(S)*-4-(Acetoxy)-1-phenyl-1-pentanone 9.

Following the same procedure described above for the preparation of (+)-*(R)*-**9**, treatment of a solution of (+)-*(S)*-**7** (0.050 g, 0.28 mmol) in anhydrous pyridine (2.0 ml) with Ac_2O (0.5 ml) afforded pure (-)-*(S)*-**9** (0.045 g, 73% yield) as a solid, m.p. 34-35°C, $[\alpha]_D^{20}$= -3.61 (*c* 0.95, $CHCl_3$).

Lipase-Catalyzed Transesterification of γ-HKs (±)-4 and (±)-7.

The following procedure is typical. Supported lipase-PS (0.20 g)[8] was added to a solution of the racemic γ-HK (±)-**4** (0.044 g, 0.20 mmol) in a 7:3 mixture of VA/THF (5 ml) (entry 1, Table 1) and the resulting suspension was stirred at 250 rpm at 37°C for 3 h. Dilution with AcOEt, and evaporation of the filtered organic solution afforded a crude reaction product (0.046 g, analyzed by ^{1}H NMR and GC to give the conversion ratio shown in Table 1), which was subjected to flash chromatography. Elution with an 8:2 mixture of hexane and AcOEt afforded pure γ-HK (+)-*(1S,2R)*-**4** (0.021 g, 96% yield),[4] $[\alpha]_D^{20}$= +17.26 (*c* 0.73, $CHCl_3$) (ee >99%), and acetate (-)-*(1R,2S)*-**6** (0.023 g, 88% yield), $[\alpha]_D^{20}$= -31.92 (*c* 0.73, $CHCl_3$) (ee

>99%). In all the other cases, the two chromatography fractions (see above) were analyzed by chiral HPLC or GC, as described in the introduction of this Section.

The crude reaction products from alcohol (±)-**7** were subjected to semipreparative TLC (an 8:2 mixture of hexane and AcOEt was used as the eluant). Extraction of the faster moving band afforded purified enriched mixtures of the non-racemic acetates (+)-*(R)*- and (-)-*(S)*-**9** which were analyzed by the chiral HPLC technique.

In the case of lipase AK (Table 1, entry 7 and Table 2, entry 11), a literature procedure was followed.[12]

(-)-*(1R,2S)*-2-(Benzoylmethyl)-1-cyclohexanol 4.

A solution of acetate (-)-*(1R,2S)*-**6** (> 99% ee) (0.037 g, 0.14 mmol) in MeOH (2 ml), was treated with K_2CO_3 (0.039 g, 0.28 mmol) and the reaction mixture was stirred for 3 h at r.t. Dilution with water (8 ml) and extraction with ether afforded pure γ-HK (-)-*(1R,2S)*-**4** (0.030 g, 82% yield)[4] (ee > 99%), $[\alpha]_D^{20}$= -17.15 (*c* 0.85, $CHCl_3$). Anal.Calcd for $C_{14}H_{18}O_2$: C, 77.08; H, 8.25. Found: C, 77.26; H, 8.01.

(+)-*(1S,2R)*-2-(Benzoylmethyl)-1-(benzoyloxy)-cyclohexane 10.

A solution of γ-HK (+)-*(1S,2R)*-**4** (0.045 g, 0.21 mmol) in anhydrous CH_2Cl_2 (4 ml) was treated with benzoyl chloride (0.05 ml, 0.42 mmol) and 4-(dimethylamino)-pyridine (DMAP) (0.040 g, 0.32 mmol) and the reaction mixture was stirred 42 h at r.t. Dilution with CH_2Cl_2 and evaporation of the washed (10% aqueous HCl, saurated aqueous K_2CO_3 and brine) afforded a crude product which was subjected to semipreparative TLC (a 7:3 mixture of hexane and AcOEt was used as the eluant). Extraction of the most intense band afforded pure (+)-*(1S,2R)*-**10** (0.042 g, 62% yield) as a liquid, $[\alpha]_D^{20}$= +40.72 (*c* 0.97, $CHCl_3$): ^{1}H NMR δ 7.85-7.98 (m, 4H), 7.32-7.48 (m, 6H), 4.79-4.90 (m, 1H), 3.19 (dd, 1H, *J*=16.1 and 4.2 Hz), 2.75 (dd, 1H, *J*=16.1 and 8.5 Hz), 2.40-2.60 (m, 1H), 2.10-2.20 (m, 1H), 1.94-2.05 (m, 1H), 1.60-1.90 (m, 2H), 1.20-1.60 (m, 4H); ^{13}C NMR δ 200.17, 166.85, 137.77, 133.61, 133.52, 128.79, 77.98, 42.33, 39.72, 32.62, 32.25, 30.37, 25.81, 25.29. UV (CH_3OH, 0.98 mg ml^{-1}) λ_{max} (nm) (ϵ_{max}, $M^{-1}cm^{-1}$): 234 (10000), 276 (900); CD (CH_3OH, 0.98 mg mL^{-1}) λ_{max} (nm) ($\Delta\epsilon_{max}$, $M^{-1}cm^{-1}$): 225 (-3.0), 234 (0.0), 243 (+2.6). Anal.Calcd for $C_{21}H_{22}O_3$: C, 78.27; H, 6.82. Found: C, 78.51; H, 7.04.

References and Notes

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(6) The substantial amount of hexamethyldisilazane (HMDS), present in the crude reaction products when washing with 5% aqueous HCl was omitted (see Experimental Section), transforms the OH-free γ-HKs into the corresponding *O*-TMS derivatives simply as a result of standing and/or warming slightly.

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