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# Enantioselective ketoester reductions in water: a comparison between microorganism- and ruthenium-catalyzed reactions

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Dedicated to Professor Henri Kagan on the occasion of his 80th birthday

ABSTRACT

In the search for green chemistry methods for the enantioselective reduction of ketoesters *Saccharomyces cerevisiae*- and ruthenium-catalyzed reactions in water have been investigated. The highest enantiomeric excesses for the reduction of α- and β-ketoesters have been obtained by *S. cerevisiae*. Chiral ruthenium catalysts are active for the reduction of all ketoesters with low to moderate enantioselectivities depending on the nature of the substrate and ligand. Interestingly, for several substrates both enantiomers of the hydroxyesters have been obtained according either to the catalytic method or to the structure of the ligand.



## 1. Introduction

Chiral alcohols are widely used building blocks which have numerous applications for the synthesis of pharmaceuticals and agrochemicals. Nowadays, methodologies following the criteria of green chemistry such as the use of safe reagents and solvents, the recyclability of catalysts, and the easy separation of reaction products are required for the preparation of chiral compounds.[1] Both organometallic and biological enantioselective catalysts have been developed as complementary tools for the reduction of ketones. Asymmetric transfer hydrogenation (ATH) has many advantages for the easy preparation of enantiomerically enriched alcohols avoiding the use of hydrogen gas under high pressure.[2] In recent years ATH reactions in water have focused increasing interest.[3] In this area we have studied catalysts for ATH reduction of ketones in water and reported on ruthenium-based catalysts which are reusable both with the same substrate or changing the ketone for each reduction without a loss of enantioselectivity.[4] Furthermore a variety of ligands were compared in multi-substrate one-pot reductions in order to optimize the catalyst.[5] We selected aminoindanol and a prolinamide ligand derived from aminoindanol as the most enantioselective ligands for ruthenium-catalyzed reductions of aromatic ketones in water.

Biocatalyses are alternative methods to perform reactions under mild conditions with high enantioselectivities and have been widely employed for the preparation of chiral alcohols.[6,7] In such a context, we have investigated enzymatic resolution through lipase-catalyzed acylation for the production of secondary chiral alcohols and improved the selectivities of the reaction by the optimization of various parameters such as the nature of substrates, acylating agents, or additives.[8]

The comparison between enantioselective bio- and metal-catalyzed reactions has rarely been examined.[9] The bioreduction of ketones using *Daucus carota L.* has been the focus of a recent review and the results compared with those given by several chemical catalysts. We thus decided to evaluate the ruthenium catalysts that we have previously studied for the enantioselective reduction of ketoesters in water in order to compare them with a biocatalyzed reaction under similar conditions. *Saccharomyces cerevisiae* was selected as a readily available, cheap enzymatic catalyst, widely used for the preparation of chiral molecules for 20 years,[10] and for the enantioselective reduction of ketones as well as of ketoesters.[11]

## 2. Results and discussion

In order to compare both the activities and the enantioselectivities of *S. cerevisiae* as a biocatalyst and of ruthenium complexes for the reduction of ketoesters in water, we selected a variety of substrates **1–13** including aliphatic and aromatic α-ketoesters, pantolactone, acyclic and cyclic β-ketoesters (see Table 1). The reaction with *S. cerevisiae* was first optimized for the asymmetric reduction of methyl benzoylformate **1**. In a buffered aqueous solution (pH 7) at 30 °C after 2 h a total conversion into the (*R*)-enantiomer of the corresponding α-hydroxyester was observed. Reduction was highly enantioselective since the (*S*)-isomer was not detected (Table 1, entry 1a). The above-mentioned conditions have been

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employed for the reduction of the other substrates by *S. cerevisiae*. Reduction with ethyl benzoylformate **2** afforded similarly high enantiomeric excess (>99%) (entry 2a) while the reduction of an aliphatic α-ketoester and ketopantolactone was less enantioselective (entries 3a and 5a). The presence of a trifluoro group was detrimental to the enantioselectivity since ethyl trifluoromethylpyruvate afforded the racemic hydroxy ester (compare entries 3a and 4a). The reduction of linear β-ketoesters **7, 8** catalyzed by *S. cerevisiae* furnished products with enantiomeric excesses of over 80% (entries 7a and 8a) but the presence of chlorine led to a nearly racemic β-hydroxyester (entry 9a). The reduction of cyclic β-ketoesters **11–13** delivered the *cis* isomer selectively (entries 11a and 12a) or in a very large amount (entry 13a). High enantioselectivities have been observed for all of these substrates especially for the reduction of β-ketoester **11** including a five-membered ring (entry 11a, only enantiomer (*R,S*) could be detected). Substrates **1–8** could thus be reduced in good yields using *S. cerevisiae* but asymmetric inductions were highly dependent upon the substrates and low enantioselectivities were observed for substrates containing halogen atoms.

**Table 1**
Enantioselective reduction of ketoesters catalyzed by *Saccharomyces cerevisiae* or by ruthenium complexes

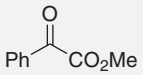
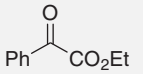
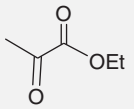
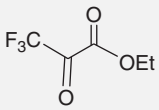
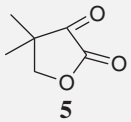
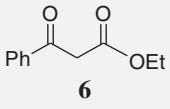
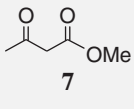
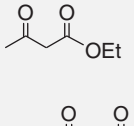
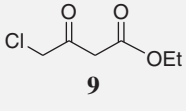
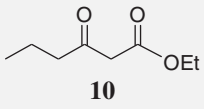
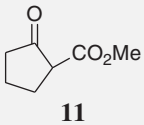
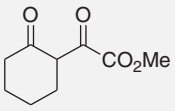
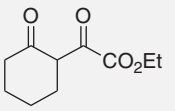
| Entry | Substrate | Catalyst[a] | *t* (h) | Yield[b] (%) | *cis*/*trans*[c] | Ee[d] (%) | Conf[e] |
|---|---|---|---|---|---|---|---|
| 1a |  **1** | *S.C* | 2 | 80 | | >99[f] | (*R*) |
| 1b | | **L¹** | 4 | 69 | | 77 | (*S*) |
| 1c | | **L²** | 48 | 71 | | 5 | (*S*) |
| 1d | | **L³** | 40 | 65 | | 13 | (*R*) |
| 2a |  **2** | *S.C* | 2 | 76 | | >99[f] | (*R*) |
| 2b | | **L¹** | 4 | 69 | | 60 | (*S*) |
| 2c | | **L²** | 48 | 62 | | 30 | (*S*) |
| 2d | | **L³** | 40 | 72 | | 13 | (*R*) |
| 3a |  **3** | *S.C* | 4 | 68 | | 93 | (*S*) |
| 3b | | **L¹** | 4 | 78 | | 10 | (*S*) |
| 3c | | **L²** | 24 | 76 | | 11.5 | (*S*) |
| 3d | | **L³** | 24 | 74 | | 11 | (*S*) |
| 4a |  **4** | *S.C* | 2 | 63 | | 5 | |
| 4b | | **L¹** | 18 | 52 | | 3 | |
| 4c | | **L²** | 24 | 75 | | 10 | |
| 4d | | **L³** | 24 | 70 | | 15 | |
| 5a |  **5** | *S.C* | 2 | 60 | | 69.5 | (*R*) |
| 5b | | **L¹** | 2 | 82 | | 66 | (*R*) |
| 5c | | **L²** | 2 | 79 | | 35 | (*R*) |
| 5d | | **L³** | 40 | 61 | | 77 | (*R*) |
| 6a |  **6** | *S.C* | 168 | 51 | | 83 | (*S*) |
| 6b | | **L¹** | 4 | 72 | | 38 | (*R*) |
| 6c | | **L²** | 48 | 66 | | 70 | (*R*) |
| 6d | | **L³** | 40 | 76 | | 81 | (*S*) |
| 7a |  **7** | *S.C* | 24 | 74 | | 91.5 | (*S*) |
| 7b | | **L¹** | 16 | 80 | | 20 | (*R*) |
| 7c | | **L²** | 40 | 71 | | 15 | (*R*) |
| 7d | | **L³** | 168 | 64 | | 3 | (*R*) |
| 8a |  | *S.C* | 16 | 78 | | 83 | (*S*) |
| 8b | | **L¹** | 16 | 71 | | 25 | (*R*) |
| 8c | | **L²** | 48 | 69 | | 15 | (*R*) |
| 8d | | **L³** | 168 | 59 | | 4 | (*R*) |
| 9a |  **9** | *S.C* | 2 | 73 | | 9 | (*S*) |
| 9b | | **L¹** | 4 | 68 | | 5 | |
| 9c | | **L²** | 20 | 61 | | 30 | (*R*) |
| 9d | | **L³** | 72 | 62 | | 3 | |
| 10a |  **10** | *S.C* | 16 | 72 | | 90 | (*S*) |
| 10b | | **L¹** | 16 | 81 | | 17.5 | (*S*) |
| 10c | | **L²** | 72 | 68 | | 4 | (*S*) |
| 10d | | **L³** | 24 | 79 | | 29 | (*S*) |
| 11a |  **11** | *S.C* | 2 | 79 | >99[f] | >99[f] | (*R,S*) |
| 11b | | **L¹** | 2 | 82 | >99[f] | 43 | (*S,R*) |
| 11c | | **L²** | 20 | 67 | >99[f] | 25 | (*S,R*) |
| 11d | | **L³** | 78 | 65 | 96/4 | 10 | (*S,R*) |

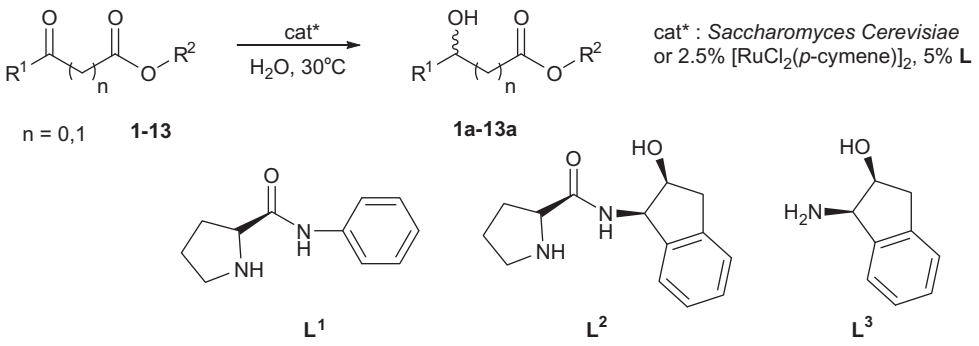
**Table 1** (*continued*)

| Entry | Substrate | Catalyst[a] | *t* (h) | Yield[b] (%) | *cis*/*trans*[c] | Ee[d] (%) | Conf[e] |
|---|---|---|---|---|---|---|---|
| 12a |  | *S.C* | 16 | 72 | >99[f] | 87 | (*R*,*S*) |
| 12b | | **L**$^1$ | 4 | 77 | 87/13 | 59 (60)[g] | (*S*,*R*) |
| 12c | | **L**$^2$ | 48 | 76 | 95/5 | 76 (50)[g] | (*S*,*R*) |
| 12d | | **L**$^3$ | 48 | 71 | 88/12 | 17 (40)[g] | (*S*,*R*) |
| | **12** | | | | | | |
| 13a |  | *S.C* | 16 | 69 | 96/4 | 88 (99)[g] | (*R*,*S*) |
| 13b | | **L**$^1$ | 2 | 76 | 66/34 | 57 (80)[g] | (*S*,*R*) |
| 13c | | **L**$^2$ | 48 | 78 | 92/8 | 70 (10)[g] | (*S*,*R*) |
| 13d | | **L**$^3$ | 48 | 60 | 93/7 | 53 (59)[g] | (*S*,*R*) |
| | **13** | | | | | | |

[a] Reactions were performed with 3 g baker's yeast and 30 mL phosphate buffer pH 7 for 1 mmol substrate or with 2.5% $[RuCl_2(p\text{-cymene})]_2$ and 5% ligand **L** in water at 30 °C, for total conversion.
[b] Isolated yield.
[c] *cis*/*trans* ratio determined by GC.
[d] Ee determined by chiral GC or HPLC of the product or of the 1-naphthoyl ester of the product.
[e] Absolute configuration of the major enantiomer was assigned by comparison with the literature.
[f] Only one peak was observed.
[g] Ee *cis* (ee *trans*).

During our previous studies we have found that a ruthenium complex coordinated with *N*-phenyl prolinamide **L**$^1$ was an enantioselective catalyst for the reduction of aromatic ketones.[4] Multi-substrate screening of ruthenium-catalyzed reactions led to the selection of two ligands *N*-aminoindanol prolinamide **L**$^2$ and aminoindanol **L**$^3$ which afforded high enantiomeric excesses for different types of ketones.[5] We have now investigated the asymmetric reduction of α- and β-ketoesters using ruthenium complexes coordinated with ligands **L**$^1$–**L**$^3$ (Scheme 1). The results are gathered in Table 1. Reactions were performed using 5 mol % catalyst and furnished total conversions into hydroxyesters using α- and β-ketoesters as substrates with reaction times depending on the ligand. Reactions were faster with *N*-phenylprolinamide **L**$^1$ than with *N*-aminoindanolprolinamide **L**$^2$ and aminoindanol **L**$^3$. The linear benzoyl formic acid esters **1** and **2** were reduced with good enantioselectivities using *N*-phenylprolinamide **L**$^1$ while ligands **L**$^2$ and **L**$^3$ gave poor results (entries 1b–1d and 2b–2d). Interestingly, α-hydroxyesters **1a** and **2a** provided by ruthenium complexes coordinated with **L**$^1$ have an (*S*)-configuration while the biocatalyst furnished the (*R*)-enantiomer (entries 1a and 1b, 2a and 2b). Unfortunately, the reduction of substrates **3** and **4** with ruthenium catalysts led to the α-hydroxyester with low enantiomeric excesses, whatever ligand was employed (entries 3b–3d, 4b–4d). The α-hydroxyester **5a** was isolated with enantiomeric excesses from 35% to 77% using ruthenium complexes (entries 5b–5d) with the same configuration (*R*) as that given by *S. cerevisae*. The ligand aminoindanol **L**$^3$ was the most enantioselective with asymmetric induction superior to that given by the biocatalyst. Reduction of aromatic β-ketoester **6** with ruthenium complexes gave the product **6a** with moderate to good enantiomeric excesses (38–81%) (entries 6b–6d). For this substrate aminoindanol **L**$^3$ was the most enantioselective ligand and gave the same major enantiomer in shorter reaction times than *Saccharomyces cerevisae* while the opposite configuration predominated with other ligands.

The ruthenium-catalyzed reduction of aliphatic linear β-ketoesters, **7–10**, afforded low asymmetric inductions (ee <30%) in all cases (entries 7b–7c, 8b–8c, 9b–9c, 10b–10c) with the three ligands **L**$^1$–**L**$^3$. In the case of aliphatic linear β-ketoesters variations in the size of ester group or in the length of the chain did not improve the enantiomeric excess. As in the biocatalyzed reaction, a ruthenium-catalyzed reduction of the cyclic β-ketoester **11** yielded the *cis* isomer selectively (entries 11b–11d) or in very large amounts (entries 12b–12d and 13b–13d). While β-hydroxyester **11a** including a five-membered ring was obtained with low enantiomeric excesses whatever ligand was employed, reduction of substrates **12** and **13** was more selective. For β-hydroxyesters **12a** and **13a** the highest enantiomeric excess was recorded with *N*-aminoindanol prolinamide **L**$^2$ ligand (entries 12c and 13c), the major configuration in this case (*S, R*) being opposite to that given by *S. cerevisae*. No variation of asymmetric induction between the reduction of methyl ester **12** and ethyl ester **13** was found with the biocatalyst and ruthenium catalysts coordinated with **L**$^1$ and **L**$^2$ ligands. Surprisingly, an increase in enantiomeric excesses of the two diastereoisomers of the ethyl β-hydroxyester **13a** was




**Scheme 1.**

observed compared to the methyl ester **12a** for reactions involving aminoindanol $\mathbf{L^3}$.

As a general trend the reduction of the various α- and β-ketoesters catalyzed by *S. cerevisae* gave higher enantiomeric excesses than ruthenium complexes except for ketopantolactone **5** which was reduced with similar enantioselectivities with both types of catalysts. However, ruthenium complexes afforded interesting asymmetric inductions (>70% ee) in some cases, such as aromatic α-ketoesters **1** and **2**, pantolactone **5**, aromatic β-ketoester **6**, and cyclic β-ketoesters **12** and **13**. As expected reductions of aromatic α- and β-ketoesters were more enantioselective than the corresponding aliphatic molecules. Different ligands gave the best results according to the structure of the substrate, phenyl prolinamide $\mathbf{L^1}$ for aromatic α-ketoesters **1** and **2**, ligand $\mathbf{L^2}$ for cyclic β-ketoesters **12** and **13**, and aminoindanol $\mathbf{L^3}$ for ketopantolactone **5** and aromatic β-ketoester **6.** The presence of a trifluoromethyl group or a chlorine atom was detrimental to the enantioselectivity with both types of catalysts. Interestingly, for several substrates both enantiomers could be obtained using either *S. cerevisae* or ruthenium complex (aromatic α- and β-ketoesters **1** and **2** and cyclic β-ketoesters **11–13**). In the case of β-ketoester **6** using *N*-aminoindanol prolinamide $\mathbf{L^2}$ and aminoindanol $\mathbf{L^3}$ as ligands furnished, respectively, (*R*) and (*S*) as major enantiomers with good enantiomeric excesses.

## 3. Conclusion

This comparison between enantioselective biocatalyzed and ruthenium-catalyzed reduction of ketoesters in water reveals several interesting characteristics. For several families of substrates good asymmetric inductions have been obtained as well as being enantiocomplementarity with biocatalysts.[12] Since the enantiomeric excesses are dependent on the substrates and ligands, the optimization of the catalyst could be envisaged for the different families of α- and β-ketoesters. The work-up is very simple for both procedures with an easy separation of the product from the catalyst. Since ligands are provided by the chiral pool and ruthenium catalysts can be recycled,[4] aryl ketoesters and cyclic β-ketoesters reductions afford products with complementary configurations using inexpensive chiral sources. Although until now *S. cerevisae* furnishes higher asymmetric inductions than ruthenium catalysts in most cases, the possibility of working on a larger scale with the latter should lead to their development for interesting applications in the future.

## 4. Experimental

### 4.1. General

Ligands $\mathbf{L^1}$ and $\mathbf{L^2}$ were synthesized according to the literature procedures.[13] Ligand $\mathbf{L^3}$ and catalyst precursor $[RuCl_2(p\text{-cymene})]_2$ and substrates were commercially available. Saccharomyces C type II was purchased from SIGMA.

Bruker AM 250 and AM 360 spectrometers, operating at 250 and 360 MHz for $^1H$, and at 62.5 and 90.6 MHz for $^{13}C$, were used for the NMR spectra. Optical rotations were determined using a Perkin–Elmer 241 Polarimeter at room temperature using a cell of 1 dm length and $\lambda = 589$ nm. HPLC analyses were performed on a Thermo Separation Product Pompe P100 with a UV detector and a chiral stationary-phase column Chiralcel OD-H. GC analyses were performed on Fisons 9000 apparatus equipped with a Chiraldex β-PM column (50 m × 0.25 mm) or a Supelco β-Dex 225 column and hydrogen as carrier gas (1.0 mL/min). All of the crude products were purified by preparative thin layer chromatography on Silica Gel 60 $PF_{254}$ (heptane/ethyl acetate 50/50).

### 4.2. General procedure for catalytic reactions

In a Schlenk tube, a solution of $[RuCl_2(p\text{-cymene})]_2$ (15.5 mg, 0.025 mmol) and ligand (0.05 mmol) in 4 mL of water was stirred at 30 °C for 1 h. Sodium formate (0.68 g, 10 mmol) and substrate (1 mmol) were then added and the solution was maintained at 30 °C until total reduction of the ketone, as monitored by TLC (reaction times reported in Table 1). Organic products were then extracted with hexane (2 × 8 mL) and dried over $MgSO_4$. After concentration, the product was purified by thin layer chromatography with hexane/ethyl acetate mixtures and spectral data compared with the literature.

### 4.3. General procedure for biocatalytic reactions

A suspension of baker's yeast (3 g) in buffer solution (pH 7) (30 mL) was maintained at 30 °C for 15 min. Then, the substrate (1 mmol) was gradually added and the mixture vigorously stirred at 30 °C. Progress of the reduction was monitored by TLC (reaction times reported in Table 1). The reaction mixture was extracted several times with $CH_2Cl_2$. After drying over anhydrous $MgSO_4$ the solvent was evaporated under reduced pressure.

#### 4.3.1. (*R*)-Methyl-2-hydroxy-2-phenylacetate 1a

HPLC (Chiralcel OD-H, hexane/*i*-PrOH: 90/10, 1.0 mL/min, $\lambda = 254$ nm): $t_S = 7.57$ min, $t_R = 13.07$ min. $[\alpha]_D^{20} = -134$ (*c* 1.0, MeOH) for 99% ee, Lit $[\alpha]_D = -143$ (*c* 1.0, MeOH).[14]

#### 4.3.2. (*R*)-Ethyl-2-hydroxy-2-phenylacetate 2a

HPLC (Chiralcel OD-H, hexane/*i*-PrOH: 90/10, flow 1.0 mL/min, $\lambda = 254$ nm): $t_S = 6.4$ min, $t_R = 11.2$ min. $[\alpha]_D^{20} = -132$ (*c* 0.9, $CHCl_3$) for 99% ee, Lit $[\alpha]_D = -134$ (*c* 1.0, MeOH, ee = 90%).[14]

#### 4.3.3. (*S*)-Ethyl 2-hydroxypropanoate 3a

Enantiomers of **3a** could not be separated by chiral HPLC or GC. After reaction the reduction products were transformed in naphthoyl esters. To a solution of alcohol **3a** (1 mmol) in $CH_2Cl_2$ were added a few mg DMAP, triethylamine (10 mg, 1 mmol), naphthoyl chloride (190 mg, 1 mmol). After stirring overnight, the solution was extracted with $CH_2Cl_2$, and after drying over $MgSO_4$, the solvent was evaporated under reduced pressure. The product was purified by thin layer chromatography with hexane/ethyl acetate mixture (70/30).

#### 4.3.4. 1-(Ethoxycarbonyl)ethyl 2-naphthoate

HPLC (Chiralcel OD-H, hexane/*i*-PrOH: 95/5, flow 0.5 mL/min, $\lambda = 254$ nm): $t_1 = 14.10$ min, $t_2 = 19.32$ min.

#### 4.3.5. Ethyl 3,3,3-trifluoro-2-hydroxypropanoate 4a

After reaction product **4a** was transformed in a naphthoyl ester and purified as described above.

#### 4.3.6. 1-(Ethoxycarbonyl)-2,2,2-trifluoroethyl 1-naphthoate

HPLC (Chiralcel OD-H, hexane/*i*-PrOH: 98/2, flow 0.5 mL/min, $\lambda = 254$ nm): $t_1 = 11.08$ min, $t_2 = 13.67$ min.

#### 4.3.7. (*R*)-Dihydro-3-hydroxy-4,4-dimethylfuran-2(3*H*)-one 5a

GC (ChiralDex β-PM, *T* (°C) column = 110 °C): $t_S = 56.8$ min, $t_R = 62.4$ min.

#### 4.3.8. (*S*)-Ethyl 3-hydroxy-3-phenylpropionate 6a

HPLC (Chiralcel OD-H, hexane/*i*-PrOH: 90/10, flow 0.5 mL/min, $\lambda = 254$ nm): $t_S = 15.1$ min, $t_R = 20.9$ min. $[\alpha]_D^{20} = -35.2$ (*c*, 0.5, $CHCl_3$) for 83% ee, Lit $[\alpha]_D = +43.7$ (*c* 1.4, $CHCl_3$)].[15]

#### 4.3.9. (*S*)-Methyl-3-hydroxybutanoate 7a

Reaction product **7a** was transformed into naphthoyl ester and purified as described above.

#### 4.3.10. 1-(Methoxycarbonyl)propan-2-yl 1-naphthoate

HPLC (Chiralcel OD-H, hexane/*i*-PrOH: 90/10, flow 0.5 mL/min, $\lambda$ = 254 nm): $t_1$ = 14.8 min, $t_2$ = 15.77 min.

#### 4.3.11. (*S*)-Ethyl 3-hydroxybutanoate 8a

Reaction product **8a** was transformed into naphthoyl ester and purified as described above.

#### 4.3.12. 1-(Ethoxycarbonyl)propan-2-yl 1-naphthoate

HPLC (Chiralcel OD-H, hexane/*i*-PrOH: 90/10, flow 0.5 mL/min, $\lambda$ = 254 nm): $t_1$ = 14.0 min, $t_2$ = 15.3 min.

#### 4.3.13. (*S*)-Ethyl 4-chloro-3-hydroxybutanoate 9a

Reaction product **9a** was transformed in naphthoyl ester and purified as described above.

#### 4.3.14. 1-(Ethoxycarbonyl)-3-chloropropan-2-yl 1-naphtoate

HPLC (Chiralcel OD-H, hexane/*i*-PrOH: 90/10, flow 0.5 mL/min, $\lambda$ = 254 nm): $t_1$ = 13.3 min, $t_2$ = 14.7 min.

#### 4.3.15. (*S*)-Ethyl 3-hydroxyhexanoate 10a

Reaction product **10a** was transformed in naphthoyl ester and purified as described above.

#### 4.3.16. 1-(Ethoxycarbonyl)pentan-2-yl 2-naphthoate

HPLC (Chiralcel OD-H, hexane/*i*-PrOH: 99/1, flow 0.5 mL/min, $\lambda$ = 254 nm): $t_1$ = 24.22 min, $t_2$ = 26.88 min.

#### 4.3.17. (*R,S*)-Methyl-2-hydroxycyclopentanecarboxylate 11a

GC (Supelco β-Dex225, (*T* column = 110 °C)): $d_1$ ($t_1$ = 21.8 min, $t_2$ = 22.6 min), $d_2$ ($t_1$ = 25.6 min, $t_2$ = 26.6 min). $[\alpha]_D^{20} = +15$ (*c*, 1.95, $CHCl_3$) for 99% ee, Lit $[\alpha]_D$ = +15.8 (*c*, 3.5, $CHCl_3$)].[16]

#### 4.3.18. (*R,S*)-Methyl-2-hydroxycyclohexanecarboxylate 12a

HPLC (Chiralcel OD-H, hexane/*i*-PrOH: 99/1, flow 0.5 mL/min, $\lambda$ = 215 nm): $d_1$ ($t_1$ = 23.03 min, $t_2$ = 28.42 min), $d_2$ ($t_1$ = 39.15 min, $t_2$ = 49.47 min).

#### 4.3.19. (*R,S*)-Ethyl-2-hydroxycyclohexanecarboxylate 13a

HPLC (Chiralcel OD-H, min hexane/*i*-PrOH: 95/5, flow 0.5 mL/min, $\lambda$ = 215 nm): $d_1$ ($t_1$ = 10.4 min, $t_2$ = 11.3 min), $d_2$ ($t_1$ = 12.5 min, $t_2$ = 13.65).

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