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Enzymatic Resolution of 3-Substituted-4-oxoesters.

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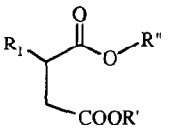
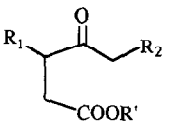
Abstract : The lipase catalyzed hydrolysis of cyanomethyl 3-substituted-4-oxoesters was studied. With 3-methyl substituted esters, PPL led to optically active compounds. When the 3-substituent was a larger group, more satisfactory results were obtained with PL, especially if the substituent attached to the ketone function is other from methyl.

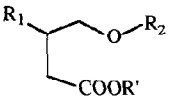
We reported previously that lipase catalyzed hydrolysis of some succinates and aspartates led with high enantiomeric excesses to optically active esters.[1] The reaction was applied to the preparation of lignan intermediates.[2] Except for aspartates, in these reactions hydrolysis of the ester function β to the chiral center was observed. We decided to investigate whether the replacement of the ester function α to the stereogenic center by another group would still result in enzymatic recognition.



Succinates



4-oxoesters

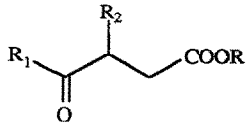


5-oxaesters

We chose 4-oxoesters, which are useful and widely used synthetic intermediates.[3] There are few reports in the literature concerning the preparation of optically active 4-oxoesters. Recently the Michael addition of lithiated chiral aminocyanides to α,β-unsaturated esters [4] was published. Also specific 4-oxoesters have been reported [5] sometimes with excellent enantiomeric excesses. Optically active 4-aldoesters are also known.[5d,6]

Preparation of 4-oxoesters

The methyl and cyanomethyl 4-oxoesters used in this study (scheme 1) were prepared by the following pathways.

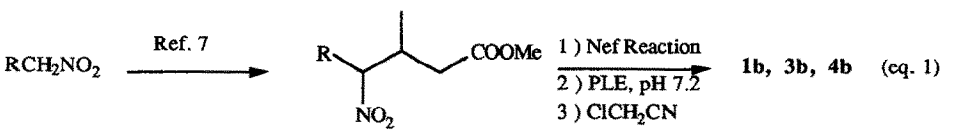


	1	2	3	4	5	6	7	8	9	10
R_1	Me	Et	C_5H_{11}	CH_2Ph	Ph	Me	Et	Me	$(CH_2)_3$	$(CH_2)_4$
R_2	Me	Me	Me	Me	Me	CH_2Ph	CH_2Ph	3-butenyl		

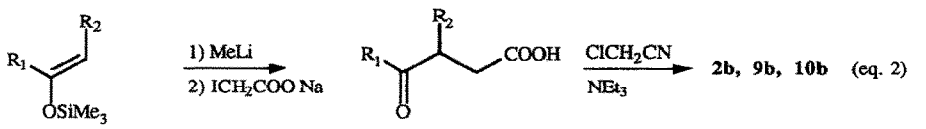
a : R=CH_3
b : R=CH_2CN
c : R=H

Scheme 1

Derivatives **1**, **3**, and **4** were obtained by the Michael addition of nitro compounds with methyl crotonate,[7] followed by a Nef reaction.[8] The resulting methyl 4-oxoesters were hydrolyzed (PLE) to give the corresponding racemic acids which were subsequently transformed into the cyanomethyl esters **1b**, **3b**, and **4b**. (eq. 1)

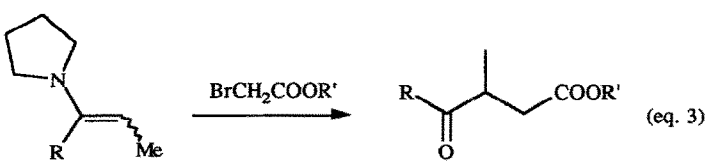


The oxoesters **2b**, **9b**, and **10b** were obtained by alkylation of the corresponding ketone enolates with sodium iodoacetate, followed by esterification of the acids **2c**, **9c**, and **10c**. (eq. 2)



2c, 9c, 10c

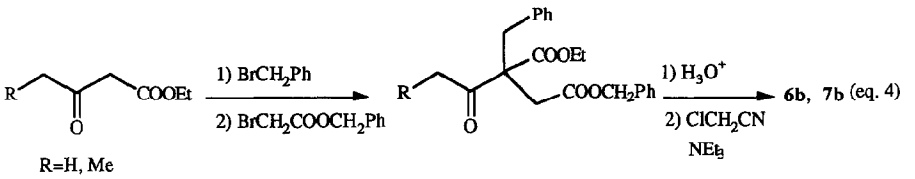
Alkylation of enamine **11a** with methyl bromoacetate gave the ketoester **2a**, while alkylation of enamine **11b** with cyanomethyl bromoacetate gave the ester **5b**. (eq. 3)



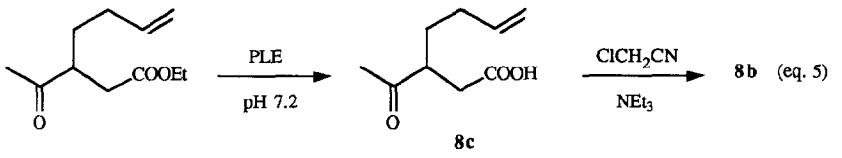
R=Et : **11a**
R=Ph : **11b**

2a : R'= Me
5b: R'= CH_2CN

Alkylation of ethyl acetylacetate and ethyl propionylacetate sequentially with benzylbromide and with benzyl bromoacetate led to the corresponding compounds with a quaternary carbon atom, which were transformed into 4-oxoacids **6c**, and **7c**. Subsequent reactions with chloroacetonitrile gave the esters **6b**, and **7b**. (eq. 4)



Ester **8b** was prepared in two steps by PLE catalyzed hydrolysis of ethyl 3-acetyl-6-heptenoate [9] followed by esterification of the acid **8c**. (eq. 5)

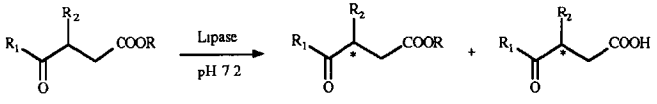


Enzymatic resolution of esters 1a, 2a, and 1b-10b

Enzymatic hydrolyses of racemic esters **1a**, **2a**, and **1b-10b** were performed at room temperature at pH 7.2. To check the absence of fast spontaneous hydrolysis, the racemic esters were stirred in water for 15 min before addition of the enzyme (no pH change). Two lipases were used for these hydrolysis; the lipase from *Pseudomonas cepacia* (PL) and the lipase from pig pancreas (PPL). Immediately after the lipase addition, the hydrolysis started and the pH was automatically maintained at 7.2 by addition of a 2M sodium hydroxide solution (pH-stat). When the desired conversions were reached (~ 50%), the remaining esters **1a**, **2a** and **1b-10b** were extracted with ether. The aqueous layers containing the sodium salts of acids **1c-10c** were acidified (pH 2) and extracted with ether. The enantiomeric excesses of the remaining esters **1a**, **2a** and **1b-10b** and of the acids **1c-10c** (after their transformation into methyl esters **1a-10a** by reaction with CH_2N_2) were measured by ^1H NMR spectroscopy using Eu(hfc)$_3$ as chiral shift reagent. Our results are reported in Table 1.

The configurations of these esters and acids were determined by chemical correlation. Oxidation of optically active methyl esters **1a-7a** by the action of trifluoroperacetic acid led generally to a mixture of the two esters **A** et **B** by a regioselective oxygen insertion with retention of configuration.[10] (scheme 2) With the esters **1a**, **2a**, **6a** and **7a** we observed mainly formation of products corresponding to the insertion of the oxygen in the more substituted position (**B** regioisomer). Usually we have compared these esters (or derivatives) with compounds of known absolute configuration by ^1H NMR spectroscopy in the presence of Eu(hfc)$_3$. For the esters **1a** and **2a** the major **B** regioisomers were compared with respectively the acetate and the propanoate prepared from the commercially available (*R*)-methyl 3-hydroxybutanoate. The **A** regioisomers of esters **3a**, **4a**, **5a** and **7a** were transesterified with methyl alcohol and the resulting compounds were compared with either authentic (*R*)-dimethyl methylsuccinate [1] (compounds **3a**, **4a** and **5a**) or authentic (*S*)-dimethyl benzylsuccinate [1] (compound **7a**). The determination of the configuration of compound **6a** was less straightforward. The acetoxyester **6aB** was reduced with $LiAlH_4$ to a diol which was acetylated and compared with the diacetate obtained in the same way from the regioisomer **7aB**. (eq. 6)

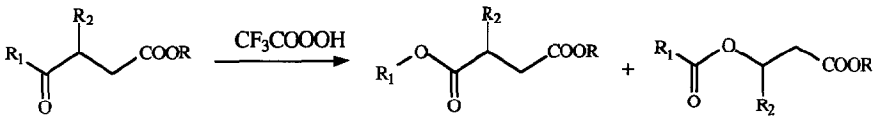
Table 1. Enzymatic Resolution of Racemic 4-Oxoesters 1a-10a, 1c, 2c.



	1	2	3	4	5	6	7	8	9	10
R_1	Me	Et	C_5H_{11}	CH_2Ph	Ph	Me	Et	Me		
R_2	Me	Me	Me	Me	Me	CH_2Ph	CH_2Ph	3-butenyl	$(CH_2)_3$	$(CH_2)_4$

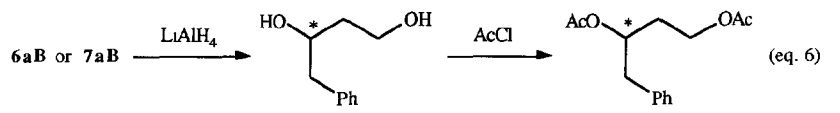
Entry	Substrate	Reaction Conditions				Optically Active Ester			Optically Active Acid		
		Enzyme	Substrate [a] / Enzyme	Reactn Time (h)	Convn (%)	Yield (%)	Ee (%)	Confign	Yield (%)	Ee (%)	Confign
1	(±)-**1a**	PPL	1	93	52	47	17	*R*	48	13	*S*
2	(±)-**1b**	PPL	0.9	1.5	50	41	53	*R*	43	43	*S*
3	(±)-**1b**	PL	0.9	3	52	44	0	-	43	0	-
4	(±)-**2a**	PPL	1	24	33	40	38	*R*	40	80	*S*
5	(±)-**2a**	PL	0.9	41	47	46	39	*R*	46	41	*S*
6	(±)-**2b**	PPL	1	2	55	44	**93**	*R*	49	**80**	*S*
7	(±)-**2b**	PL	0.9	1.2	54	42	15	*R*	47	11	*S*
8	(±)-**3b**	PPL	1	1	50	49	**>98**	*R*	49	**85**	*S*
9	(±)-**4b**	PPL	1	3	60	49	**>95**	*R*	49	**85**	*S*
10	(±)-**5b**	PPL	0.33	10	59	45	55	*R*	48	38	*S*
11	(±)-**5b**	PL	1	8	50	45	56	*R*	46	55	*S*
12	(±)-**6b**	PPL	0.25	32	50	43	43	*S*	45	35	*R*
13	(±)-**6b**	PL	0.125	24	20	49	64	*S*	44	16	*R*
14	(±)-**7b**	PPL	0.5	7	55	49	28	*S*	40	26	*R*
15	(±)-**7b**	PL	0.66	11	54	43	**>98**	*S*	45	**81**	*R*
16	(±)-**8b**	PPL	0.5	6	51	37	34	b	45	22	b
17	(±)-**8b**	PL	0.5	2	60	37	49	b	43	27	b
18	(±)-**9b**	PPL	1	0.5	30	40	0	-	39	0	-
19	(±)-**10b**	PPL	1	2	82	45	46	(*R*)[c]	45	10	(*S*)[c]
20	(±)-**10b**	PL	1	3	50	40	6	(*R*)[c]	44	8	(*S*)[c]

[a] Weight/weight. [b] The configurations (not determined) were opposite for PPL and PL. [c] Postulated absolute configuration.



	A regioisomer	B regioisomer
1a	1.5 %	98.5 %
2a	42 %	58 %
3a	62 %	38 %
4a	95 %	5 %
5a	90 %	10 %
6a	0	100 %
7a	38 %	62 %

Scheme 2



The absolute configuration of acid **10c** was postulated to be (*S*) after comparison of chiroptical properties of its methyl ester with those of the known ethyl ester.[11]

Discussion

Results reported in Table 1 show that the rates of hydrolysis with PPL of compounds **1a** and **2a** (methyl esters) were low. We found that this rate could be increased by hydrolysis of their cyanomethyl esters. Besides, this actived group was interesting since we observed an improvement of the enantiomeric excesses (compare entries 1, 2 and 4, 6). Such a cyanomethyl effect had been already observed [2] with this enzyme, while with PL this effect seemed low (entries 5, 7). With compounds **1-5** possessing a methyl group fixed on the chiral carbon atom, we observed with PPL an improvement of the enzymatic recognition when the size of the substituent R_1 fixed on the ketone function increased. The (*S*) isomer was the main substrate of this enzyme. In the hydrolysis of dimethyl methylsuccinate the same isomer reacts preferencially.[1] With PPL, when the size of the substituent fixed on the stereogenic carbon center increased (compounds **6**, **7** and **8**), we observed a decrease of the chiral recognition (entries 12, 14, and 16). The (*R*) isomer became the main substrate in the hydrolysis of compounds **6**, **7**. Interestingly in the hydrolysis of dimethyl benzylsuccinate [1] the (*R*) isomer was also the best substrate. However for ester **7b** we found it was better to choose PL. Comparison of the results observed with esters **6b** and **7b** (entries 13 and 15), shows that with PL it seems more efficient to have a substituent different from methyl. Low enzymatic recognition of enantiomers was observed in the case of cyclic 4-oxoesters **9**, **10**. (entries 18-20)

In all cases, the ee's of the acids measured were lower than the expected values based on the NaOH consumption (10-20% less). Two main reasons could be *a priori* proposed to explain these results: either a

chemical hydrolysis of the cyanomethyl esters at pH 7.2 (this could be ruled out by the fact that no spontaneous hydrolysis of the esters was observed in water) or more probably, a partial racemization of the sodium salts of the acids during the enzymatic reactions.

In conclusion, this study shows that the preparation of optically active 3-substituted-4-oxoesters is possible using enzymes. These results are interesting since chemical methodologies seem to have only limited possibilities.[4,5] When the 4-oxoesters have a methyl present on the stereogenic carbon atom, PPL appears the choice enzyme, while when the 4-oxoesters have two substituents different from methyl it appears better to use PL. It could be noted that a low enzymatic recognition of enantiomers was observed during the hydrolysis of 5-oxaesters.[12] Thus it seems (with the two lipases studied) that for a good enantiodifferentiation of esters possessing a β stereogenic center, at least a polar or a polarizable group is necessary.

Experimental Section

General. ^1H NMR spectra were recorded at 200 MHz. Mass spectra were determined at an ionizing voltage of 70 eV. Column chromatography was performed with silica gel (70-230 Mesh). TLC was performed on 0.25 mm Silica gel (Merck 60 F 254). Dry solvents were obtained as follows: diethyl ether was distilled over $LiAlH_4$, THF was distilled over sodium-benzophenone and hexane over P_2O_5. Other reagents were distilled before use. PLE (acetone powder) and PPL were purchased from Sigma. The lipase from *Pseudomonas cepacia* was obtained from Amano.

Methyl 3-methyl-4-oxopentanoate 1a: The Michael addition of methyl crotonate with nitroethane has been already reported.[7] The subsequent Nef reaction was performed using a described procedure [8] to give ester **1a** [13] (70% yield, bp 94°C/12 mmHg).

Cyanomethyl 3-methyl-4-oxopentanoate 1b: Hydrolysis of ester **1a** was made using the acetone powder of pig liver by a procedure already described.[14] Starting from 4 g of ester **1a**, we obtained 3.3 g of acid **1c** [15] (92% yield). The acid (3.3 g, 0.0254 mol) was added to a mixture of THF (100 mL), cyanomethanol [16] (1.45 g, 0.0254 mol) and DCC (5.3 g, 0.0254 mol). After completion of the reaction at room temperature (monitored by tlc) the solvent was removed under vacuum. The residue was taken off with ether and filtered over Celite. After concentration, the ester **1b** was purified by distillation (3.65 g, 85% yield) bp: 76°C/0.05 mmHg ; IR (neat): 1760 (CO), 1718 (CO), 1360, 1150 cm^{-1}; ^1H NMR δ: 4.78 (d, J = 15.8 Hz, 1H), 4.65 (d, J = 15.8 Hz, 1H), 3.05 (m, 1H), 2.85 (dd, J = 9.5 and 17 Hz, 1H), 2.40 (dd, J = 5.2 and 17 Hz, 1H), 2.25 (s, 3H), 1.22 (d, J = 7.4 Hz, 3H); Anal. Calcd for $C_8H_{11}O_3N$: C, 56.80 ; H, 6.55. Found: C, 57.01 ; H, 6.59.

Methyl 3-methyl-4-oxohexanoate 2a: Heating under reflux in benzene (120 mL) for 6 h of N-(2-penten-3-yl)pyrrolidine [17] (9.4 g, 0.062 mol) with methyl bromoacetate (9.37 g, 0.061 mol) gave an alkylated product which was hydrolyzed with water (50 mL). After distillation of the organic solvent, the crude mixture was diluted with ether (100 mL) and washed successively with 1M HCl (2x50 mL) and water (3x25 mL). The combinated aqueous phases were extracted with ether (3x50 mL) and the resulting organic phase was washed as precedently. All the organic phases were combined, dried (Na_2SO_4) and concentrated. Distillation gave the methyl ester **2a** [18] (5.07 g, 51.6% yield) bp 62°C/0.01 mmHg.

3-Methyl-4-oxohexanoic acid 2c: The trimethylsilyl enol ether obtained from 3-pentanone [19] (1.2 g, 7.5 mmoles) was added at 10°C to a THF solution (2 mL) of methyllithium (9.4 mmol). After 30 min at 10°C the

solution was cooled at -50°C and sodium iodoacetate was added rapidly (1.6 g, 7.7 mmol). The reaction mixture was warmed at room temperature and acidified (pH 4) with cold 1M HCl. After ether extraction (4x10 mL) the organic phase was dried (Na_2SO_4) and concentrated to give acid **2c** [20] (0.80 g, 74% yield).

Cyanomethyl 3-methyl-4-oxohexanoate 2b: A mixture of 0.80 g of acid **2c** (5.5 mmol), triethylamine (16.5 mmol), and chloroacetonitrile (22 mmol) in CH_2Cl_2 (20 mL) was heated overnight under reflux. 0.2M HCl (5 mL) was added and after 10 min. the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (2x5 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under vacuum. The crude mixture was purified by liquid chromatography (SiO_2, ether) to give ester **2b** (0.87 g, 83% yield). IR (neat): 2960, 1750 (CO), 1710 (CO), 1160 cm^{-1}; ^1H NMR δ: 4.78 (d, J = 15.8 Hz, 1H), 4.64 (d, J = 15.8 Hz, 1H), 3.15 - 2.95 (m, 1H), 2.86 (dd, J = 9.0 and 16.6 Hz, 1H), 2.71 - 2.47 (m, 2H), 2.39 (dd, J = 4.8 and 16.6 Hz, 1H), 1.19 (d, J = 7.6 Hz, 3H), 1.06 (t, J = 7.7 Hz, 3H); EI-MS m/z: 183 (M^+), 127, 126, 113, 84, 57 (100); Anal. Calcd for $C_9H_{13}O_3N$: C, 59.00; H, 7.15. Found: C, 59.22 ; H, 7.11.

Methyl 3-methyl-4-oxononanoate 3a: This ester [21] was prepared in two steps using the sequence reported for the preparation of ester **1a** (70% overall yield), bp 100°C/0.1 mmHg.

Cyanomethyl 3-methyl-4-oxononanoate 3b: Hydrolysis of ester **3a** using the procedure reported for the ester **1a** gave the corresponding acid **3c** [22]. (91% yield). This acid was esterified using chloroacetonitrile (see the preparation of ester **2b**) to give the cyanomethyl ester **3b** (90% yield), bp 110°C/0.1 mmHg. IR (neat) : 2960, 1745 (CO), 1720 (CO), 1200, 1005 cm^{-1}; ^1H NMR δ: 4.78 (d, J = 15.8 Hz, 1H), 4.64 (d, J = 15.8 Hz, 1H), 3.13 - 2.95 (m, 1H), 2.87 (dd, J = 9.3 and 16.8 Hz, 1H), 2.68 - 2.39 (m, 2H), 2.39 (dd, J = 4.2 and 16.8 Hz, 1H), 1.70 - 1.48 (m, 2H), 1.42 - 1.22 (m, 6H), 1.18 (d, J = 7.5 Hz, 3H), 0.90 (t, J = 7.5 Hz, 3H) ; EI-MS m/z: 225 (M^+), 169, 112, 99 (100), 84, 71, 55, 43; Anal. Calcd for $C_{12}H_{19}O_3N$: C, 63.98; H, 8.50. Found: C, 64.08 ; H, 8.61.

Methyl 3-methyl-4-oxo-5-phenylpentanoate 4a: This ester was prepared in two steps using the sequence reported for the preparation of ester **1a** (68% overall yield). The ester was purified by liquid chromatography (SiO_2, ether-hexane : 40-60). ^1H NMR δ: 7.40 - 7.12 (m, 5H), 3.87 (s, 2H), 3.66 (s, 3H), 3.18 - 3.04 (m, 1H), 2.70 ((dd, J = 9.4 and 17 Hz, 1H), 2.31 (dd, J = 4.9 and 17 Hz, 1H), 1.13 (d, J = 8 Hz, 3H); Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.95; H, 7.39.

Cyanomethyl 3-methyl-4-oxo-5-phenylpentanoate 4b: Hydrolysis of ester **4a** with PLE (see the preparation of acid **1c**) led to the acid **4c** (88% yield) which was esterified using chloroacetonitrile (see the preparation of ester **2b**) to give the cyanomethylester **4b**. IR (neat) : 2980, 1760 (CO), 1718 (CO), 1165, 1045 cm^{-1}; ^1H NMR δ: 7.42 - 7.18 (m, 5H), 4.72 (d, J = 15.8 Hz, 1H), 4.60 (d, J = 15.8 Hz, 1H), 3.83 (s, 2H), 3.27 - 3.08 (m, 1H), 2.88 (dd, J = 8.9 and 16.9 Hz, 1H), 2.40 (dd, J = 4.6 and 16.9 Hz, 1H), 1.19 (d, J = 7.4 Hz, 3H); EI-MS m/z: 245 (M^+), 189, 154, 126, 91, 84, 65; Anal. Calcd for $C_{14}H_{15}O_3N$: C, 68.56; H, 6.16. Found: C, 68.66 ; H, 6.21.

Cyanomethyl 3-methyl-4-oxo-4-phenylbutanoate 5b: This ester was prepared by reaction of N-(1-phenyl-1-propen-1-yl)pyrrolidine [17] with cyanomethyl bromoacetate following the procedure reported for the synthesis of ester **2a** (48% yield). ^1H NMR δ: 8.02 - 7.95 (m, 2H), 7.67 - 7.47 (m, 3H), 4.77 (d, J = 15.7 Hz, 1H), 4.66 (d, J = 15.7 Hz, 1H), 4.08 - 3.89 (m, 1H), 3.08 (dd, J = 8.7 and 17.1 Hz, 1H), 2.58 (dd, J = 5.2 and 17.1 Hz, 1H), 1.30 (d, J = 7.2 Hz, 1H); EI-MS m/z: 231 (M^+), 174, 105 (100), 77, 51; Anal. Calcd for $C_{13}H_{13}O_3N$: C, 67.52; H, 5.67. Found: C, 67.63 ; H, 5.73.

3-Benzyl-4-oxopentanoic acid 6c: Alkylations of ethyl acetoacetate with benzylbromide then with benzyl bromoacetate following a reported procedure [23] led to the corresponding ketoester (85% overall yield). The crude ketoester (0.1 mol) was heated 20 h at reflux in a mixture of conc. HCl (150 mL) and CH_3COOH (20 mL) to give the acid **6c** (87% yield). ^1H NMR δ: 12.5 (m, 1H), 7.45 - 7.15 (m, 5H), 3.48 - 2.35 (m, 5H), 2.22 (s, 3H).

Cyanomethyl 3-benzyl-4-oxopentanoate 6b: Following the procedure described for the preparation of ester **2b**, the ester **6b** was obtained and purified by distillation, bp 175°C/0.1 mmHg. 70% yield. IR (neat): 1760 (CO), 1720 (CO), 1150, 1040, 700 cm^{-1}; ^1H NMR δ: 7.40 - 7.11 (m, 5H), 4.72 (d, J = 15.6 Hz, 1H), 4.58 (d, J = 15.6 Hz, 1H), 3.40 - 3.23 (m, 1H), 3.03 (dd, J = 6.3 and 13.5 Hz, 1H), 2.85 (dd, J = 9.7 and 17.3 Hz, 1H), 2.61 (dd, J = 8.5 and 13.5 Hz, 1H), 2.40 (dd, J = 4.2 and 17.3 Hz, 1H), 2.17 (s, 3H) ; EI-MS *m/z*: 245 (M^+), 147, 145, 117, 91, 65, 43 (100); Anal. Calcd for $C_{14}H_{15}O_3N$: C, 68.56; H, 6.16. Found: C, 68.48 ; H, 6.28.

3-Benzyl-4-oxohexanoic acid 7c: This acid was prepared following the procedure reported for the preparation of acid **6c** (76% yield), bp 180°C/0.1 mmHg. ^1H NMR δ: 7.40 - 7.09 (m, 5H), 3.32 - 3.14 (m, 1H), 2.95 - 2.15 (m, 6H), 1.00 (t, J = 7.6 Hz, 3H); EI-MS *m/z*: 220 (M^+), 202, 173, 161, 145, 117, 91, 57 (100)

Cyanomethyl 3-benzyl-4-oxohexanoate 7b: This ester was obtained from acid **7c** by the procedure reported for the preparation of ester **2b** (80% yield), bp 165-170°C/0.1 mmHg. IR (neat): 1765 (CO), 1720 (CO), 1150, 705 cm^{-1}; ^1H NMR δ: 7.40 - 7.10 (m, 5H), 4.72 (d, J = 15.6 Hz, 1H), 4.58 (d, J = 15.6 Hz, 1H), 3.38 - 3.20 (m, 1H), 3.02 - 2.80 (m, 2H), 2.70 - 2.25 (m, 4H), 1.02 (t, J = 7.5 Hz, 3H); EI-MS *m/z*: 259 (M^+), 241, 173, 161, 145, 117, 91, 57 (100); Anal. Calcd for $C_{15}H_{17}O_3N$: C, 69.48; H, 6.61. Found: C, 69.71 ; H, 6.50.

3-Acetyl-6-heptenoic acid 8c: This acid was obtained by PLE hydrolysis of ethyl 3-acetyl-6-heptenoate [9]. ^1H NMR δ: 12.00 - 13.00 (m, 1H), 5.90 - 5.68 (m, 1H), 5.18 - 4.97 (m, 2H), 3.13 - 2.92 (m, 1H), 2.79 (dd, J = 8.9 and 17 Hz, 1H), 2.43 (dd, J = 4 and 17 Hz, 1H), 2.23 (s, 3H), 2.18 - 2.00 (m, 2H), 1.87 - 1.65 (m, 1H), 1.65 - 1.40 (m, 1H) (90% yield).

Cyanomethyl 3-acetyl-6-heptenoate 8b: This ester was prepared from acid **8c** following the procedure reported for the preparation of ester **2b** (90% yield), bp 110°C/0.1 mmHg ^1H NMR δ: 5.90 - 5.68 (m, 1H), 5.12 - 4.98 (m, 2H), 4.77 (d, J = 15.8 Hz, 1H), 4.64 (d, J = 15.8 Hz, 1H), 3.15 - 2.98 (m, 1H), 2.85 (dd, J = 8.9 and 17 Hz, 1H), 2.49 (dd, J = 4 and 17 Hz, 1H), 2.28 (s, 3H), 2.19 - 2.00 (m, 2H), 1.88 - 1.45 (m, 2H); Anal. Calcd for $C_{11}H_{15}O_3N$: C, 63.14; H, 7.23. Found: C, 63.39 ; H, 7.40.

Cyanomethyl (2-oxocyclopentyl)acetate 9b: This ester was prepared from (2-oxocyclopentyl)acetic acid [24] following the procedure reported for the preparation of ester **2b** (71% yield).^1H NMR δ: 4.76 (s, 2H), 2.92 - 2.73 (m, 1H), 2.63 - 2.00 (m, 6H), 2.00 - 1.50 (m, 2H); Anal. Calcd for $C_9H_{11}O_3N$: C, 59.66; H, 6.12. Found: C, 59.81; H, 6.27.

Cyanomethyl (2-oxocyclohexyl)acetate 10b: This ester was prepared from (2-oxocyclohexyl)acetic acid [25] following the procedure reported for the preparation ester **2b** (83% yield). ^1H NMR δ: 4.78 (d, J = 15.8 Hz, 1H), 4.68 (d, J = 15.8 Hz, 1H), 3.00 - 2.75 (m, 2H), 2.52 - 2.05 (m, 5H), 2.00 - 1.36 (m, 4H); EI-MS *m/z*: 195 (M^+), 152, 139, 138, 110, 97, 84, 82, 68, 55 (100); Anal. Calcd for $C_{10}H_{13}O_3N$: C, 61.53; H, 6.71. Found: C, 61.68; H, 6.83.

Enzymatic resolution of esters 1a, 2a, 1b-10b: In an erlenmeyer flask were placed water (10 mL) and the racemic ketoester (1 mmol). The pH was adjusted to 7.2 with 2M NaOH and the enzyme was added (see Table 1 for the amounts of crude PL and PPL). The reaction started immediately. After NaOH consumption corresponding to the conversion reported in Table 1 (monitored using a pH stat) had been observed, the mixture was extracted with ether (4 x 10 mL). The organic phase was dried (Na_2SO_4) and concentrated to give the remaining ester which was purified by liquid chromatography (SiO_2). The aqueous phase was acidified with 1M HCl (pH 2), then extracted with ether (5 x 10 mL). The etheral phase was dried (Na_2SO_4) and concentrated to give the carboxylic acid which was esterified (CH_2N_2). The methyl ester was then purified by liquid chromatography (SiO_2). The results are reported in Table 1. The following $[\alpha]_D$ values have been measured: (*R*)-**1b** $[\alpha]_D$ +25.3 (c 2.3, THF), ee 53%; (*S*)-**1a** $[\alpha]_D$ -28.3 (c 1.5, THF), ee 43%; (*R*)-**2b** $[\alpha]_D$ +21.8 (c 1.85, THF), ee 93%; (*S*)-**2a** $[\alpha]_D$ -34.8 (c 1.6, THF), ee 81%; (*R*)-**3b** $[\alpha]_D$ +22.6 (c 3.7, THF), ee 92%; (*S*)-**3a** $[\alpha]_D$ -30.1 (c 2.9, THF), ee 85%; (*R*)-**4b** $[\alpha]_D$ +12.9 (c 1.6, THF), ee> 95%; (*S*)-**4a** $[\alpha]_D$ -10.9 (c 3, THF), ee 85%; (*R*)-**5b** $[\alpha]_D$ -10.1 (c 5, THF), ee 48%; (*S*)-**5a** $[\alpha]_D$ -1.0 (c 1.6, THF), ee 39%; (*R*)-**6b** $[\alpha]_D$ -28.6 (c 1.8, THF), ee 44%; (*S*)-**6a** $[\alpha]_D$ +30.5 (c 2.3, THF), ee 35%; (*S*)-**7b** $[\alpha]_D$ -72.8 (c 6.5, THF), ee > 98%; (*R*)-**7a** $[\alpha]_D$ +86.6 (c 1.4, THF), ee 81%. LPP hydrolysis of the cyanomethyl **8b** gave the remaining ester with an $[\alpha]_D$ of -18.8 (c 1.8, THF), ee 34%. After reaction of the acid **8c** with diazomethane, the $[\alpha]_D$ measured for the methyl ester **8a** was +14.3 (c 1.6, THF), ee 22%. LP hydrolysis of ester **8b** gave opposite signs for the $[\alpha]_D$ of the cyanomethyl and methyl esters (see Table 1 for the ee values).

Baeyer-Villiger reaction of esters 1a-7a: A mixture of CH_2Cl_2 (0.75 mL), 90 µl of 30% H_2O_2, and 0.674 mL of trifluoroacetic anhydride was stirred 30 min at 0°C. The ketoester (3 mmol) in CH_2Cl_2 (2 mL) was added in 10 min. After 2-15 h at room temperature, the mixture was concentrated under vacuum and the residue purified by liquid chromatography (SiO_2: ether-hexane). Yields : 90-97%. The results of the different oxidations are reported in scheme 2. In the case of ketoesters **3a, 4a, 5a, 7a**, the succinates **A** were transesterified into methylesters: the mixte succinate **A** (3 mmol) was added to a MeOH solution (5 mL) containing 10 drops of $SOCl_2$ and stirred 20 h at room temperature. The mixture was concentrated under vacuum and the residue was purified by liquid chromatography (SiO_2). The resulting dimethyl methylsuccinate was studied by ^1H NMR spectroscopy using Eu(hfc)$_3$ as chiral shift reagent and compared with an authentic sample of partially enriched (*R*)-dimethyl methylsuccinate.[1]

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