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Synthesis of enantiomerically pure bicyclic condensed δ-lactones via microbial reduction and enzymic resolution strategies

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Abstract

The formation of enantiopure δ-lactones condensed with alicyclic rings has been achieved either by reduction with baker's yeast of the corresponding δ-keto esters and δ-keto acids or by enzymic resolution of the former compounds. The absolute configurations of the lactones were determined by means of CD spectroscopy, using the correlation method.

1. Introduction

Biological methods which make use of whole cell microorganisms or purified enzymes are widely present in the literature for the synthesis of chiral building blocks.[1] Among the biocatalysts used for the asymmetric reduction of prochiral carbonyl groups, baker's yeast plays the most traditional and useful role,[2] although stereoselectivity this is not always satisfactory and needs improvement by thermal pretreatment,[3] addition of inhibitors,[4] presence of organic solvent,[5] immobilization on a solid phase[6] and eventually isolation of reductases from the microorganism.[7] Keto acids and esters are excellent substrates for baker's yeast. Although there are not as many examples as for the bioreductions of β-keto esters and acids,[1d,3,5b,6c,8a,9] bioreductions of α-,[4a,c,5b,8,7b] γ-[10] and δ-keto esters and acids[10a,b,g,h,11] have also been reported.

The use of 5-oxoalkanoic acids of the C_8–C_{12} chain as substrates for baker's yeast reduction for the production of δ-lactones was first reported by Tuynenburg Muys and co-workers.[10a] Later, Francke[11a] studied the reduction of 5-oxodecanoic acid and proposed a mechanism for its stereospecific conversion. However, in neither case was data reported either on the enantiomeric excess or on the absolute configurations of the products. A systematic study was undertaken by Utaka

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and co-workers[10b] on the reduction by fermenting baker's yeast of 5-oxoalkanoic acids and esters of C_6–C_{10}, C_{13}, and C_{16} chains. Apart from the first member of the series, all substrates furnished the corresponding δ-lactones with an *R* configuration in low to good yields and with >98% e.e.s. In a chemoenzymic synthesis of Leukotriene B_4, Sih and co-workers[11b] prepared a chiral 5-hydroxy ester intermediate by reduction with baker's yeast under non-fermenting conditions of *t*-butyl 5-oxo-5-(1,3-dithian-2-yl)pentanoate. In this case, the product with an *S* configuration was isolated in good yield and high enantiomeric excess (>97%). On the contrary, the analogous methyl ester derivative underwent hydrolyses by esterases of baker's yeast but the resulting 5-oxo-5-(1,3-dithian-2-yl)pentanoic acid was not reduced under the same conditions. A 5-oxopentanoic ester of a similar structure, i.e. functionalized at C_5 with a thiazole group, was subjected to bioreduction with fermenting baker's yeast to furnish the corresponding 5-hydroxy acid in *S* configuration, with >95% e.e. and good yield, as a result of a parallel hydrolysis of the methyl ester function.[10h] On reduction with non-fermenting baker's yeast, a series of 5-oxoalkanoic acids bearing a methyl group either at C_2 or C_3 afforded the corresponding δ-lactones with 100% e.e. and also with high diastereomeric excess.[11c]

From the above short survey on bioreductions of 5-oxoalkanoic acids and esters with baker's yeast it is shown that no trend was evident, which is surely related to the multienzymic nature of baker's yeast and to the reaction conditions. As a consequence, the stereoselective outcome of the reactions is absolutely unpredictable, as it is the possibility of isolating the 5-hydroxy derivative intermediates and also whether a difference exists between the reduction of δ-keto acids and that of δ-keto esters.

Other enzyme-assisted syntheses of δ-lactones, having fairly good enantiomeric excesses, were also reported. Thus, enantiomerically pure δ-lactones were obtained by enzymic resolution of their racemic forms by lipases[12] and also by the nucleophilic ring opening of enantiomerically pure alkyl oxiranes, obtained by enzyme-catalyzed kinetic resolutions.[13]

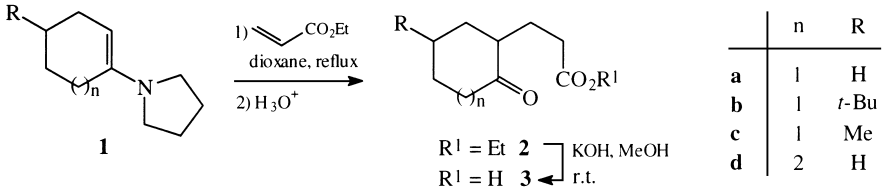
In our previous paper[14] we reported on the baker's yeast reduction of some δ-keto esters, by which enantiomerically pure condensed bicyclic δ-lactones, having excellent enantiomeric excesses, were prepared. Also, diastereoselectivity was high, allowing the use of mixtures of distereomeric esters as substrates.

Owing to the fact that δ-valerolactones condensed to a cycloalkane ring are widely present as structural subunits of polycyclic naturally occurring products, in the present paper we extend our study to other δ-keto esters derived from cycloalkanones and also to their δ-keto acid analogs, with the aim of making a comparison between the two systems.

2. Results and discussion

2.1. Synthesis of the substrates

Like the δ-keto esters **2a**[15] and **2b**,[14] **2c** and **2d** (Scheme 1) were also prepared by alkylation reaction of the corresponding enamines **1c** and **1d** with ethyl acrylate and successive hydrolysis. When R was different from hydrogen, the resulting *cis* and *trans* diastereomeric mixtures of thermodynamic formation were inseparable, the *cis*:*trans* ratio being 90:10 for **2b** and 85:15 for **2c**. By hydrolysis under basic conditions, the corresponding δ-keto acids **3a**–**d** were obtained. In the case of **3c**, the *cis*:*trans* ratio was slightly different from that of the corresponding δ-keto esters **2c**, namely 95:5.



Scheme 1.

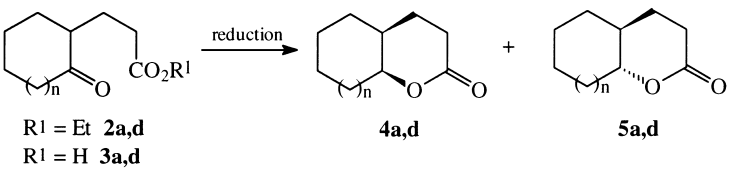
2.2. Chemical reduction of the δ-keto esters **2c,d** and δ-keto acids **3a–d**

The most significant results of the chemical and biological reductions of the δ-keto esters **2a–d** and δ-keto acids **3a–d** are listed in Table 1, while the structures of the products are shown in Schemes 2 and 3. Although the data concerning the reductions of **2a** and **2b** had already been described in a previous paper,[14] they are reported here for comparison. On reduction with sodium cyanoborohydride, **2a** furnished a 1:4 mixture of the corresponding bicyclic *cis*- and *trans*-fused δ-lactones **4a** and **5a**, (Scheme 2 and Table 1), while **2b**, which was a 9:1 mixture of *cis* and *trans* diastereomers, furnished **4b**, **5b** and **6b** in the ratio of 18:72:10 (Scheme 3 and Table 1).

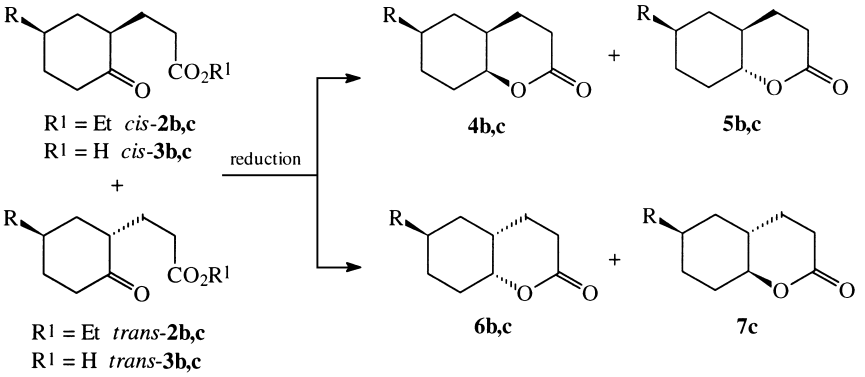
Table 1

	Reduction with $NaCNBH_3$			Reduction with raw baker's yeast[a)]			
Substrate	Yield[b)] (%)	Products	Ratio of products (%)	React. Time (days)	Conv. (%)	Products (% e.e.)[c)]	Ratio of products (%)
2a	60	**4a, 5a**	20:80	16	80	**(–)-4a** (99)	100
3a	95	**4a, 5a**	25:75	8	75	**(–)-4a** (>99), **5a** (43)	40:60
2b *cis-trans* 90:10	80	**4b, 5b, 6b**	18:72:10	12	50	**(–)-4b** (99)	100
3b *cis-trans* 90:10	95	**4b, 5b, 6b**	13:77:10	13	5	**(–)-4b** (79)	100
2c *cis-trans* 85:15	60	**4c, 5c, 6c, 7c**	10:70:8:12	10	55	**(–)-4c** (81), **(+)-5c** (60), **6c** (>99), **7c** (>99)	71:17:7:5
3c *cis-trans* 95:5	70	**4c, 5c, 6c, 7c**	15:80:1:4	17	40	**(–)-4c** (>99), **(+)-5c** (72), **6c** (>99), **7c**	65:29:4:2
2d	68	**4d, 5d**	80:20	27	40	**(–)-4d** (>99), **(–)-5d** (>99)	80:20
3d	95	**4d, 5d**	80:20	15	10	**4d, 5d**	75:25

a) b.y. incubated at 50°C for 30 min; b.y./substrate: 10 g/mmole; substrate conc.: 0.05 M in water; room temperature; b) after purification; c) Enantiomerically pure compounds lacking the sign of α were not isolated.



Scheme 2.



Scheme 3.

The reduction of the 85:15 mixture of *cis* and *trans*-**2c** was more complex. In fact, four lactones were identified in the reaction mixture after acidic treatment, namely **4c**, **5c**, **6c** and **7c** in the ratio of 10:70:8:12, respectively (Scheme 3). The stereochemical assignments were made on the basis of the chemical shift values observed for the proton at C-8a and the methyl group at C-6 in their ^{1}H and ^{13}C NMR spectra, respectively (Table 2). Table 2 also lists the resonances of H-8a for the other bicyclic δ-lactones **4a**, **4b**, **5a**, **5b** and **6b** for a comparison.

Compounds **4c** and **5c**, derived from *cis*-**2c**, while **6c** and **7c** derived from *trans*-**2c**, as shown in Scheme 3. In fact, the major product **5c** (70%) must be formed from *cis*-**2c** which was the major component in the parent mixture (85%). Since the signal of its proton at C-8a is characteristic of an axial proton ($W_H = 28.0$ Hz), the fusion between the rings must be *trans* and the methyl group at C-6 *equatorial* (21.6 ppm). The methyl group at C-6 is also *equatorial* in **4c** (22.3 ppm) as it has its proton at C-8a ($W_H = 7.1$ Hz). Therefore, lactone **4c** must also be derived from *cis*-**2c**. As a consequence, compounds **6c** and **7c** must be formed from *trans*-**2c**. Since H-8a in **7c** showed the same chemical shift value and pattern as the same proton in **5c**, the fusion between the rings must be *cis* in **6c** and *trans* in **7c**. Attempts to separate the four diastereomeric lactones by flash-chromatography resulted in the isolation of the only major compound **5c**.

Chemical reduction of the δ-keto ester **2d** under the same conditions used for **2a**–**c** afforded a 4:1 mixture of the *cis*- and *trans*-fused lactones **4d** and **5d**, respectively. This attribution was made on the basis of the chemical shift values found for H-9a for the two stereoisomers.[16] The high frequency value (4.58 ppm) was attributed to the *cis*-fused system **4d** and the low frequency value (4.01 ppm) to the *trans*-fused lactone **5d**. Chemical reductions of the δ-keto acids **3a**–**d** afforded mixtures of the corresponding lactones of about the same compositions as those found for the δ-keto esters **2a**–**d** (Table 1). Reductions of both the δ-keto esters and acids afforded the corresponding *trans*-fused lactone **5** as the major product. The exception was the reduction of the **2d** and its acid **3d** which furnished the *cis*-fused lactone **4d** as the major product.[17]

Table 2
The most relevant NMR data for δ-lactones

		^{1}H-NMR data for H-8a			^{13}C-NMR for Me at C-6	
		δ, ppm	W_H, Hz	orientation	δ, ppm	orientation
Cis-fused δ-lactones	**4a**	4.49	7.2	eq		
	4b	4.45	5.2	eq		
	4c	4.47	7.1	eq	22.3	eq
	6b	4.45	22.0	ax		
	6c	4.20	18.9	essentially axial	20.5	eq
Trans-fused δ-lactones	**5a**	3.88	26.3	ax		
	5b	3.84	26.3	ax		
	5c	3.80	28.0	ax	21.6	eq
	7c	3.80	28.0	ax	17.7	ax

2.3. *Baker's yeast reductions of the δ-keto esters **2c**, **2d** and the δ-keto acids **3a–d***

A few different reaction conditions were checked for bioreductions of the δ-keto esters **2** and δ-keto acids **3**, namely the use of untreated raw and dry baker's yeast, pretreatment of the former at 50°C for 30 min and 1 h, as well as different baker's yeast:substrate ratios, when dry baker's yeast was used. In Table 1 we report only the results obtained when raw baker's yeast preincubated at 50°C for 30 min was used, since no relevant differences were found when the other conditions were used.

Baker's yeast reduction of the keto ester **2a** had already been found[14] to be highly diastereo- and enantioselective, since the only product obtained was the δ-lactone (–)-**4a** having the *cis* fusion between the rings. On the contrary, bioreduction of the corresponding keto acid **3a** was by no means diastereoselective, as both lactones (–)-**4a** and **5a** were obtained. Furthermore, the enantiomeric excess was satisfactory only for the *cis*-fused lactone (–)-**4a**. Just with the aim of shifting the reaction towards the formation of the *trans*-fused lactones **5a**, several other reaction conditions were checked, including the use of inhibitors such as methyl vinyl ketone,[3] allyl bromide, ethyl chloroacetate and phenacylchloride,[4b] but unsuccessfully.

As to the comparison between the reductions of the δ-keto esters **2** and δ-keto acids **3**, the most striking difference was found for the system **b**. In fact, in the case of the acid **3b**, conversion was so low (5%) even after days, as to prevent the use of the reaction for a preparative scale. Probably this inhibition may be ascribed to the presence of the *t*-butyl group. In fact, no difference was found between the bioreductions of **2c** and **3c**, in which the *t*-butyl group was substituted for a methyl group. The diastereoselectivity was poor (mixtures of *cis*- and *trans*-fused lactones **4c** and **5c**, respectively, was always obtained), although enantioselectivity was in general high. In some cases, pretreatment of baker's yeast enhanced both the diastereoselectivity and the enantio-

selectivity but no trend could be evidenced. Interestingly, the formation of the *cis*-fused lactone **4c** was favoured over that of the *trans*-fused one **5c**, but the isolation of the former, which was shown by chiral HRGC analysis to have >99% e.e. was not possible.

As to the systems **2d** and **3d**, a lower conversion was observed for the δ-keto acid, although the diastereoselectivity of the reaction was fairly high (50% d.e.).

From the crude reaction mixtures also, the unreacted δ-keto esters (+)-*cis*-**2c** and (+)-**2d**, having 93 and 86% e.e., respectively, were recovered. The latter value was obtained indirectly, since racemic **2d** was not separable on the chiral columns available. Therefore, (+)-**2d** was reduced with sodium cyanoborohydride and the resulting δ-hydroxy esters were cyclized to the corresponding δ-lactones (+)-**4d** and (+)-**5d**, whose enantiomeric excesses were determined by HRGC on a chiral column.

2.4. Enzymic hydrolyses

Since baker's yeast reductions of both δ-keto esters **2c**,**d** and δ-keto acids **3a–d** afforded, in most cases, mixtures of products, and also conversions were unsatisfactory, an alternative approach was used for the synthesis of enantiomerically pure δ-lactones, namely the kinetic resolution of the δ-keto esters by hydrolytic enzymes.

The 9:1 mixture of racemic δ-keto esters *cis*- and *trans*-**2b** was resolved with Lipase PS, by which the corresponding δ-keto acid *cis*-(–)-**3b** with 70% e.e. was obtained. *Candida rugosa* lipase (CRL) also hydrolyzed the ester group but with lower e.e. (51%) and porcine pancreatic lipase (PPL), α-chymotrypsin (α-CT) and *Pseudomonas fluorescens* lipase (PFL) were not effective. Pig liver esterase (PLE), *Mucor miehei* lipase (MML), porcine liver acetone powder (PLAP), and horse liver acetone powder (HLAP) showed very poor enantioselectivities.

Better results were obtained with the 85:15 mixture of racemic *cis*- and *trans*-**2c**. Of the various enzymes which exhibited a high E value (Table 3), α-CT was the most efficient, rapidly affording the δ-keto acid *cis*-(–)-**3c** with 92% d.e. and 98% e.e. Other lipases and esterases, such as PLE, MML, PLAP, HLAP and CRL were also effective in hydrolyzing the ester group but with low or no enantioselectivity.

On the contrary, enzymic resolution of the δ-keto ester **2d** was by no means satisfactory. In fact all the enzymic systems checked were characterized by a low E value. However, α-CT and PPL ($E=5$ and 4, respectively) afforded the corresponding δ-keto acid **3d** with 66 and 57% e.e., respectively, while MML, PLAP and HLAP showed very poor enantioselectivity. The enantiomeric excesses of the unreacted ester **2d** and acid **3d** were not determined by HRGC, because neither **2d** nor its methyl ester analogue, obtained from **3d** by treatment with diazomethane, were separable on chiral chromatographic columns. Therefore, **2d** and **3d** were reduced with sodium cyanoborohydride, with the aim of determining the e.e.'s of their corresponding lactones. It should be noted, however, that the acidic conditions required for the reduction with $NaBH_3CN$ (reductions with other reducing agents were unsatisfactory) are likely to racemize partially the substrates.

2.5. Determination of the absolute configuration of the δ-lactones (–)-4c, (–)-4d, (–)-5d

The absolute configurations of the δ-lactones (–)-**4c** and (–)-**4d**, obtained by reduction of the corresponding δ-keto esters *cis*-**2c** and **2d** with baker's yeast, were determined by analysis of the CD spectra of their respective unreacted δ-keto esters *cis*-(+)-**2c** and (+)-**2d**, recovered from the bioreductions. A comparison of their CD spectra with that of the already known[14] δ-keto ester (1*S*,5*S*)-(–)-**2b** (Fig. 1) would indicate the same configuration of C-1, that is 1*S* for *cis*-(+)-**2c** and 1*R* for (+)-**2d**, the different notation being due to a different priority sequence in the two lactones.

Table 3
Enzymic resolution of the 85:15 mixture of (±)-*cis* and *trans*-**2c**

Enzyme	E	React. time (min)	Conv. (%)	*cis*-(–)-**2c** (% e.e.)	*cis*-(–)-**3c** (% e.e.)
α-Chymotrypsin (α-CT)[a)]	149	20	27	42	98
Porcine pancreatic lipase (PPL)[b)]	83	150	20	24	97
Pseudomonas fluorescens lipase (PFL)[c)]	37	70	32	44	92
Lipase PS[d)]	13	67	33	39	81

[a)]0.51 g (2.39 mmol) of (±)-**2c**, 44 mg α-CT in 26.7 ml of phosphate buffer; [b)]0.27 g (1.28 mmol) of (±)-**2c**, 192 mg PPL in 14.5 ml of phosphate buffer; [c)]0.27 g (1.28 mmol) of (±)-**2c**, 6 mg PFL in 14.5 ml of phosphate buffer; [d)]0.20 g (0.94 mmol) of (±)-**2c**, 3.8 mg Lipase PS in 14.5 ml of phosphate buffer.

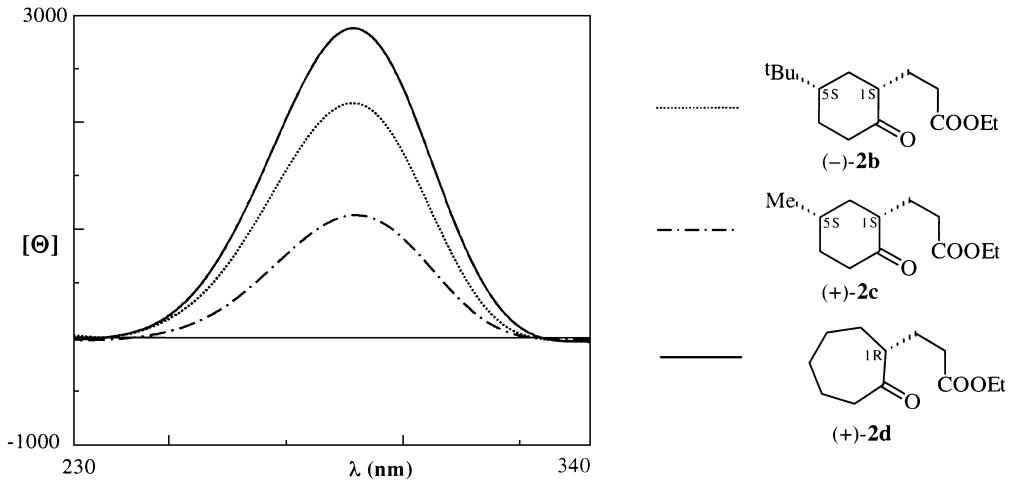
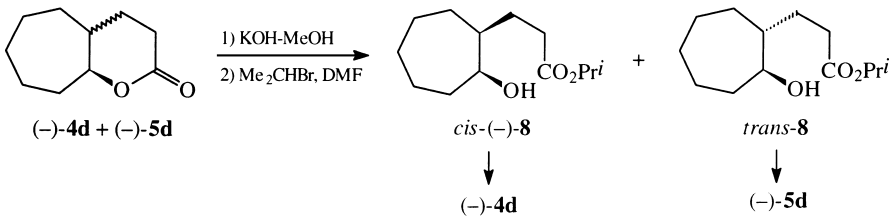


Figure 1. CD spectra of the δ-keto esters (–)-**2b**, (+)-**2c** and (+)-**2d**

Therefore, since *cis*-(*S*)-(+)-**2c** was recovered unreacted, the δ-lactone *cis*-(–)-**4c**, which was the main product (71%) of the bioreduction, must be derived from *cis*-(*R*)-(–)-**2c**. As a consequence, its absolute configuration is 4a*R*,6*R*,8a*S*. In a similar manner, the absolute configuration of (–)-**4d** was assigned as 4a*S*,9a*S*. This latter assignment was confirmed by the analysis of its CD curve. However, since lactone (–)-**4d** was inseparable from its diastereomer (–)-**5d**, the separation was effected in accordance with a literature procedure,[18] as follows. The diastereomeric mixture was

treated with KOH in methanol to open their respective lactone rings and the resulting carboxylate groups were esterified with isopropylbromide (Scheme 4). The isopropyl δ-hydroxy esters *cis*-(–)-**8** and *trans*-**8** thus obtained were separated on flash chromatography. However, only the *cis* diastereomer was obtained as pure compound, whereas the *trans* one was contaminated by 15% of the former. On heating, both hydroxy esters were reconverted separately into the corresponding δ-lactones (–)-**4d** and (–)-**5d**, this latter in admixture with the former (15%).



Scheme 4.

Although the size of the fused carbocyclic ring is different, the CD spectrum of (–)-**4d** was compared with those of the other *cis*-fused lactones (–)-**4a** and (–)-**4b**, whose absolute configurations had already been determined,[14] and with that of (–)-**4c**, whose absolute configuration has been assigned above. The curves were almost superimposable and therefore the absolute configuration of (–)-**4d** was assigned as 4a*S*,9a*S*. (Fig. 2)

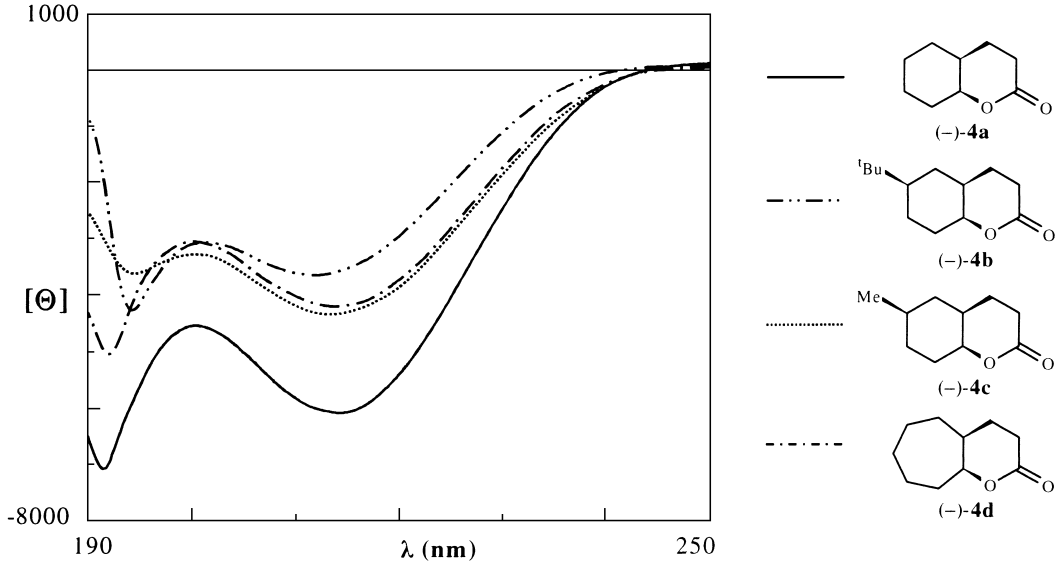
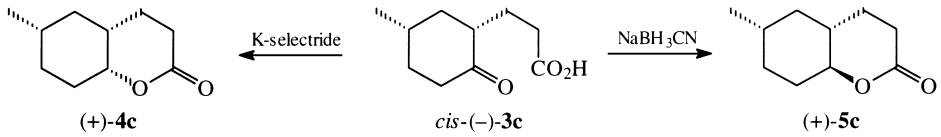


Figure 2. CD spectra of the *cis*-fused δ-lactones (–)-**4a**, (–)-**4b**, (–)-**4c** and (–)-**4d**

Since (–)-**5d** was isolated from the bioreduction of **2d** in admixture with (–)-**4d**, its absolute configuration is likely to be 4a*R*,9a*S*, differing from that of (–)-**4d** only for the configuration around C-4a. This attribution will be confirmed later by comparing the CD spectrum of (–)-**5d** with that of the *trans*-fused lactone (+)-**5c**, obtained from the δ-keto acid *cis*-(–)-**3c**.

The acid *cis*-(–)-**3c**, isolated in high optical purity from the enzymic resolution of racemic *cis*-**2c**, was assigned the 1*S*,5*S* absolute configuration by comparing its CD spectrum with that of its ethyl ester *cis*-(+)-**2c**, whose absolute configuration was determined above to be *S*. In fact both compounds exhibited a positive Cotton effect for the n→π* transition around 290 nm.

The δ-keto acid *cis*-(–)-**3c** was then reduced with both K-Selectride™ and sodium cyanoborohydride, which are known[19] to show opposite diastereopreference (Scheme 5). From the former reduction, a 9:1 mixture of (+)-**4c** and (+)-**5c** was obtained and from the latter a 15:85 mixture of the same δ-lactones. Separation by flash chromatography of the two mixtures allowed for the isolation of both diastereomers (+)-**4c** and (+)-**5c**; the former, however, contaminated with 9% of the latter.



(+)-**4c** *cis*-(–)-**3c** (+)-**5c**

Scheme 5.

The absolute configuration of (+)-**4c** is known from the previous determination made on (–)-**4c** to be 4a*S*,6*S*,8a*R* and therefore that of (+)-**5c**, which differs from (+)-**4c** for the configuration around C-8a, is 4a*S*,6*S*,8a*S*.

The *trans*-fused lactones (–)-**5b**, (+)-**5c** and (–)-**5d** exhibited CD curves which were practically superimposable (Fig. 3). As a consequence, the absolute configuration of (–)-**5d** was assigned to be 4a*R*,9a*S*.

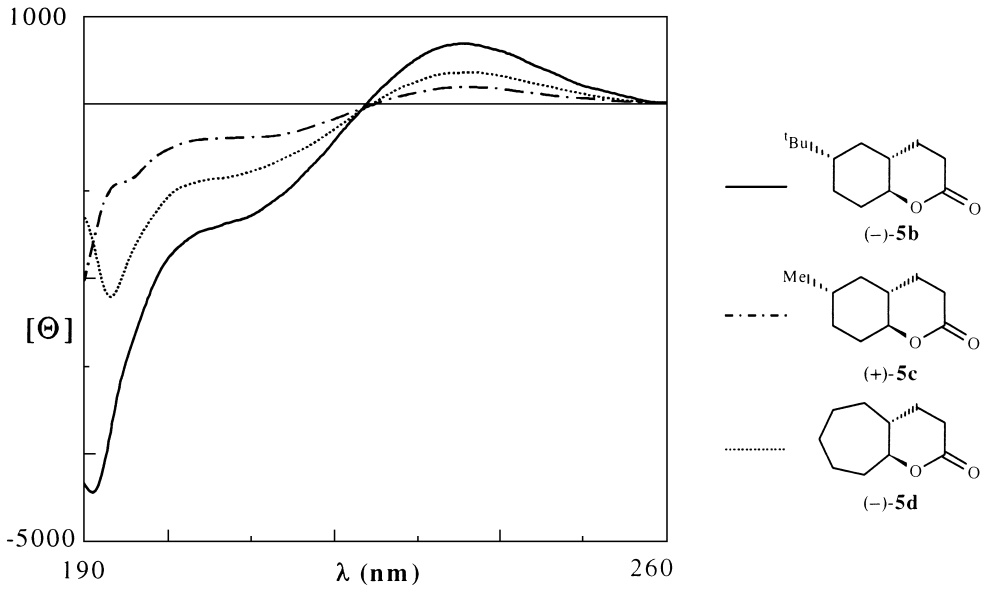


Figure 3. CD spectra of the *trans*-fused δ-lactones (–)-**5b**, (+)-**5c** and (–)-**5d**

3. Conclusions

δ-Keto acids are not as good for baker's yeast as the corresponding δ-keto ester substrates, in particular as far as conversions are concerned. This result might be related to a type of poisoning of the yeast occurring when the concentrations of 5-oxo acids or 5-hydroxy acids or both increase, as already reported by Francke[11a] for linear systems. Also, diastereoselectivity and enantioselectivity of the reactions were lower. No evidence was found which would account for the hydrolysis of the δ-keto esters to the corresponding δ-keto acids in the reaction medium prior to reduction, as suggested by some authors for the bioreduction of long chain 5-keto esters and acids.[10b] On the contrary, because our δ-keto acids are such bad substrates for baker's yeast, we are in favour of the intermediacy of δ-hydroxy esters when δ-keto esters are reduced. In any case, there is no general trend. Some molecules are better reduced as δ-keto esters, others as δ-keto acids. However, since in general bioreductions were not diastereoselective, enzyme-catalyzed kinetic resolutions of chiral racemic 5-keto esters are more advantageous, in particular when mixtures of diastereomers are to be used as substrates.

4. Experimental

4.1. General

IR spectra were recorded on a Jasco FT/IR 200 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were run on a Jeol EX-400 spectrometer (400 MHz for proton), using deuteriochloroform as a solvent and tetramethylsilane as the internal standard. Coupling constants and W_H's are given in Hz. Optical rotations were determined on a Perkin–Elmer Model 241 polarimeter. CD spectra were obtained on a Jasco J-700A spectropolarimeter (0.1 cm cell) using CH_3OH as a solvent. GLC analyses were run on a Carlo Erba GC 8000 instrument and on a Shimadzu GC-14B instrument, the capillary columns being EC-WAX (30 m×0.32 mm) (carrier gas He, 40 KPa) and a Chiraldex™ type G-TA, trifluoroacetyl γ-cyclodextrin (40 m×0.25 mm) (carrier gas He, 180 KPa) or DiMePe β-cyclodextrin (25 m×0.25 mm). Enzymic hydrolyses were performed using a pH-stat Controller PHM290 Radiometer Copenhagen. Mass spectra were recorded on a Hewlett–Packard 5971-A GC–MS instrument by the electron-impact mode. TLCs were performed on Polygram® Sil G/UV_{254} silica gel pre-coated plastic sheets (eluant: light petroleum:ethyl acetate). Flash chromatography was run on silica gel 230–400 mesh ASTM (Kieselgel 60, Merck). Light petroleum refers to the fraction with b.p. 40–70°C and ether to diethyl ether.

4.2. Synthesis of the substrates **2c** and **2d**

The δ-keto esters **2c** were prepared by reacting 1-pyrrolidinyl-4-methylcyclohexene **1c** with ethyl acrylate in refluxing dioxane for 3 h, according to the literature procedure.[15] Water was added and the mixture was refluxed for 1 h. After the usual workup, an inseparable mixture of *cis*-**2c** and *trans*-**2c** in the ratio of 85:15 was obtained.

In the same manner, the δ-keto ester **2d** was prepared starting with 1-pyrrolidinylcycloheptene **1d**.[20]

The spectroscopic data for compounds (+)-**2c** and (+)-**2d** recovered in 20% yield from their respective bioreductions, are given.

4.2.1. Ethyl (1S,5S)-(+)-3-(2-oxo-5-methylcyclohexyl)propionate cis-***2c***

IR, (film) cm^{-1}: 1710 (C=O), 1735 (CO_2); ^1H NMR, δ, ppm: 4.12 (2H, q, J = 7.3 Hz, OCH_2CH_3), 2.36 (5H, m), 2.02 (4H, m), 1.50 (1H, m), 1.35 (1H, m), 1.25 (3H, t, J = 7.3 Hz, OCH_2CH_3), 1.12 (1H, m), 1.00 (3H, d, J = 6.4 Hz, CH_3); ^{13}C NMR, δ, ppm: 212.3 (s, C=O), 173.3 (s, O–C=O), 59.9 (t, OCH_2CH_3), 48.3 (d, C-1), 42.1 (t), 41.3 (t), 35.7 (t), 31.7 (d, C-4), 31.5 (t), 24.3 (t), 21.0 (q, CH_3), 14.0 (q, OCH_2CH_3); *m/z*: 212 ($M^{+\cdot}$, 5%), 167 (32), 166 (60), 139 (17), 138 (26), 125 (13), 124 (25), 112 (12), 111 (10), 99 (11), 97 (16), 96 (27), 95 (17), 83 (16), 82 (12), 81 (20), 70 (20), 69 (18), 67 (15), 60 (10), 55 (100), 53 (15); 93% e.e. (HRGC, β-CDX), $[\alpha]_D^{25} = +8.1$ (*c* 0.32, CH_3OH), $[\Theta]_{290} = +1129$.

4.2.2. Ethyl trans-*3-(2-oxo-5-methylcyclohexyl)propionate* trans-***2c***

Although the spectra were run on the mixture, the most significant peaks are given separately. ^1H NMR, δ, ppm: 4.12 (2H, q, J = 7.3 Hz, OCH_2CH_3), 2.36 (3H, m), 2.02 (3H, m), 1.75–1.50 (4H, m), 1.25 (3H, t, J = 7.3 Hz, OCH_2CH_3), 1.06 (3H, d, J = 6.2 Hz, CH_3); ^{13}C NMR, δ, ppm: 60.0 (t, OCH_2CH_3), 46.8 (d, C-2), 39.6 (t), 37.6 (t), 33.9 (t), 26.4 (d, C-4), 25.7 (t), 19.4 (q, CH_3), 14.0 (q, OCH_2CH_3); *m/z*: 212 ($M^{+\cdot}$, 4%), 167 (30), 166 (56), 139 (15), 138 (24), 125 (14), 124 (25), 112 (11), 111 (10), 99 (11), 97 (16), 96 (28), 95 (17), 83 (17), 82 (13), 81 (20), 70 (18), 69 (15), 67 (17), 60 (11), 56 (14), 55 (100), 54 (10), 53 (16).

4.2.3. Ethyl (R)-(+)-3-(2-oxocycloheptyl)propionate ***2d***

IR, ^1H NMR and ^{13}C NMR data were identical with the reported values:[21] *m/z*: 212 ($M^{+\cdot}$, 4), 167 (32), 166 (39), 139 (16), 138 (37), 125 (14), 112 (15), 98 (19), 97 (14), 96 (13), 95 (14), 88 (18), 84 (14), 82 (13), 81 (15), 70 (13), 69 (16), 68 (13), 67 (23), 61 (11), 60 (16), 55 (100), 54 (18), 53 (14); e.e. ≥86% (determined after reduction with $NaBH_3CN$ and chiral HRGC γ-CDX analysis of the lactones obtained) $[\alpha]_D^{25} = +27.3$ (*c* 0.11, CH_3OH), $[\Theta]_{290} = +2886$.

4.3. General procedure for the hydrolysis of the δ-keto esters ***2a–d***

The δ-keto ester (1 mmol) was added to a solution of KOH (2 mmol) in methanol (1.6 ml). The mixture was stirred for 2 days, acidified with 2N HCl and extracted with ether, after evaporation of the methanol.

4.3.1. 3-(2-Oxocyclohexyl) propionic acid ***3a***

All spectroscopic data are in accordance with the literature.[22]

4.3.2. (1S,5S)-(−)-3-(2-Oxo-5-(1,1-dimethylethyl)cyclohexyl)propionic acid[23] cis-***3b***

The keto acid *cis*-(–)-**3b** was recovered from enzymic hydrolysis with Lipase PS in 20% yield. Oil; IR, cm^{-1} (film): 1725, 1710 (C=O); ^1H NMR, δ, ppm: 10.45 (1H, bs, OH), 2.40 (5H, m), 2.10 (3H, m), 1.53 (3H, m), 1.19 (1H, m), 0.91 (9H, s); ^{13}C NMR, δ, ppm: 213.2 (s, C=O), 179.6 (s, COOH), 48.5 (d), 46.9 (d), 41.5 (t), 35.3 (t), 32.3 (s, *C* $(CH_3)_3$), 31.6 (t), 28.7 (t), 27.5 (q, $(CH_3)_3$), 24.5 (t); *m/z*: 208 $(M–H_2O)]^{+\cdot}$, 72), 193 (24), 165 (19), 152 (20), 151 (22), 137 (24), 124 (69), 123 (38), 109 (20), 96 (100), 95 (46), 79 (27), 67 (41), 57 (72), 55 (51); 70% e.e. (determined by chiral HRGC β-CDX, after esterification with CH_2N_2), $[\alpha]_D^{25} = -3.4$ (*c* 0.32, CH_3OH), $[\Theta]_{288} = +663$.

4.3.3. (1S,5S)-(−)-3-(2-Oxo-5-methylcyclohexyl)propionic acid[24] cis-***3c***

The keto acid *cis*-(–)-**3c** was recovered from enzymic hydrolysis with α-CT in 24% yield (in admixture with 4% of *trans*-**3c**). IR, cm^{-1} (film): 1725, 1710 (C=O); ^1H NMR, δ, ppm: 9.44 (1H,

s, OH), 2.41 (5H, m), 2.02 (4H, m), 1.48 (1H, m), 1.38 (1H, m), 1.11 (1H, m), 1.00 (3H, d, J = 6.2 Hz, CH_3); ^{13}C NMR, δ, ppm: 213.0 (s), 179.4 (s), 48.3 (d), 42.2 (t), 41.4 (t), 35.8 (t), 31.9 (d), 31.4 (t), 24.2 (t), 21.1 (q); *m/z*:184 ($M^{+\cdot}$, 3), 166 ($M–H_2O^{+\cdot}$, 89), 138 (36), 124 (44), 109 (14), 96 (96), 95 (36), 81 (100), 68 (22), 67 (44), 55 (38); 98% e.e. (determined by chiral HRGC β-CDX, after esterification with CH_2N_2), $[\alpha]_D^{25} = -3.8$ (*c* 0.13, CH_3OH), $[\Theta]_{289} = +1479$.

4.3.4. trans-*3-(2-Oxo-5-methylcyclohexyl)propionic acid* trans-***3c***

^1H NMR, δ, ppm: 9.44 (1H, s, OH), 2.40 (5H, m), 1.95 (3H, m), 1.60 (4H, m), 1.00 (3H, d, J = 7.0 Hz, CH_3); ^{13}C NMR, δ, ppm: 214.4 (s), 178.8 (s), 46.7 (d), 39.6 (t), 37.7 (t), 33.9 (t), 31.6 (t), 26.5 (d), 25.5 (t), 19.5 (q).

4.3.5. 3-(2-Oxocycloheptyl)propionic acid[21,25] ***3d***

IR, cm^{-1} (film): 1725,1705 (C=O); ^1H NMR, δ, ppm: 9.30 (1H, s, OH), 2.60 (1H, m), 2.49 (2H, m), 2.35 (2H, m), 1.97 (1H, m), 1.85 (4H, m), 1.64 (2H, m), 1.36 (3H, m); ^{13}C NMR, δ, ppm: 216.0 (s, C=O), 178.7 (s, COOH), 50.7 (d, C-1′), 42.6 (t, C-3′), 31.4 (t, C-2), 31.3 (t, C-2′), 29.0 (t, C-3), 28.3 (t, C-4′), 26.7 (t, C-5′), 24.0 (t, C-6′); *m/z*:184 ($M^{+\cdot}$, 3), 166 ($M–H_2O]^{+\cdot}$, 100), 138 (93), 123 (14), 112 (17), 110 (33), 109 (40), 96 (37), 95 (40), 82 (36), 81 (84), 68 (41), 67 (75), 55 (51).

4.4. Reductions with baker's yeast

To a stirred suspension of 100 g of raw baker's yeast (preincubated or not) or dry baker's yeast purchased from Sigma-Aldrich (4 g/mmol or 20 g/mmol) in 200 ml of water was added the δ-keto ester (10. 0 mmol) at room temperature. The course of the reaction was monitored by HRGC. At the end of the reaction, brine was added and the broth was continuously extracted with ether for 48 h. The organic phase was dried and evaporated.

4.5. General procedure for enzymic hydrolyses

The following enzymes were used: α-Chymotrypsin (α-CT, 51.8 U/mg), *Pseudomonas fluorescens* lipase (PFL, 42.5 U/mg), and *Mucor miehei* lipase (MML) were purchased from Fluka; porcine pancreatic lipase type II (PPL), pig liver acetone powder (PLAP), horse liver acetone powder (HLAP), *Candida rugosa* lipase type VII (CRL, 700-1500 U/mg), pig liver esterase (PLE, suspension in 3.2 M $(NH_4)_2SO_4$ solution 20 mg/ml, 230 U/mg), and lipase type XII from *Pseudomonas* species (Lipase PS, 27 U/mg) were purchased from Sigma.

To a solution of 1.0 mmol of the δ-keto ester in 10 ml of phosphate buffer (pH 7.4) was added the enzyme, under vigorous stirring. The course of the reaction was monitored with a pH-STAT, with continuous addition of 1.0N NaOH. At 20% conversion, the reaction mixture was extracted with ether to separate the unreacted δ-keto ester. The mother liquors were acidified with 5% HCl and extracted with ether. The organic phase was dried on Na_2SO_4 and treated with diazomethane to esterify the carboxylic group before the HRGC analysis.

4.6. Reduction of cis-*(–)-**3c** with K-Selectride*[TM26,27]

The keto acid *cis*-(–)-**3c** (1.0 mmol) in anhydrous THF (2 ml) was added dropwise to a stirred 1.0 M solution of K-Selectride™ (1.2 equiv.) in THF, at –35°C, under an argon atmosphere. After 1.5 h, water (0.16 ml) and ethanol (0.6 ml) were added and the temperature was allowed to

warm to 0°C. The solution was then added with 6 M NaOH (0.4 ml) and 30% H_2O_2 (0.6 ml), saturated with K_2CO_3 and extracted with diethyl ether. Evaporation of the solvent furnished the δ-lactone (+)-**4c**, which was purified on flash chromatography.

*4.6.1. (4a*S*,6*S*,8a*R*)-(+)-6-Methyl-octahydro-2*H*-1-benzopyran-2-one **4c***

The title compound was obtained in 20% yield as an oil. IR, cm^{-1} (film): 1740 (C=O); ^1H NMR, δ, ppm: 4.47 (1H, m, W_H 7.1, H-8a), 2.51 (2H, t, J = 6.0 Hz, H-3), 2.08 (2H, m), 1.91 (1H, m), 1.51 (5H, m), 1.24 (1H, m), 1.08 (1H, q, J = 13.7 Hz), 0.92 (3H, d, J = 6.0 Hz, CH_3); ^{13}C NMR, δ, ppm: 172.7 (s, C=O), 77.2 (d), 34.6 (t), 32.7 (d), 31.6 (d), 30.4 (t), 27.8 (t), 26.4 (t), 24.9 (t), 22.3 (q, CH_3); *m/z*: 168 ($M^{+\cdot}$, 1), 124 (2), 111 (15), 96 (25), 95 (100), 83 (28), 82 (26), 81 (53), 68 (30), 67 (37), 55 (52); 99% e.e. (by chiral HRGC γ-CDX), $[\alpha]_D^{25} = +17.9$ (*c* 0.08, CH_3OH) (in admixture with 9% of (+)-**5c**), $[\Theta]_{192} = +5039$, $[\Theta]_{214} = +4205$.

*4.7. Reduction of **3c** with $NaBH_3CN$*

*4.7.1. (4a*S*,6*S*,8a*S*)-(+)-6-Methyl-octahydro-2*H*-1-benzopyran-2-one **5c***

Compound (+)-**5c** was obtained by reduction of (–)-**3c** with $NaBH_3CN$ in 20**%** yield after purification by flash-chromatography. IR, cm^{-1} (film): 1740 (C=O); ^1H NMR, δ, ppm: 3.79 (1H, ddd, $J_1 = 11.9$, J_2 9.9, J_3 4.4 Hz, H-8a), 2.59 (1H, part A of an ABMX system, $J_1 = 18.0$, J_2 7.3, J_3 4.0 Hz, H-3), 2.46 (1H, part B of an ABMX system, $J_1 = 18.0$, J_2 9.5, J_3 8.2 Hz, H-3), 2.02 (1H, dq, $J_1 = 12.6$, $J_2 = J_3 = J_4 = 3.7$ Hz, H-8eq), 1.84–1.70 (3H, m, H-4, H-5, H-7), 1.53–1.38 (4H, m, H-4, H-4a, H-6, H-8ax), 0.95 (1H, m, H-7), 0.85 (3H, d, J = 6.6 Hz, CH_3), 0.74 (1H, m, H-5); ^{13}C NMR, δ, ppm: 171.5 (s, C=O), 83.2 (d, C-8a), 39.3 (t, C-5), 38.1 (d, C-4a), 32.3 (t, C-7), 31.9 (t, C-8), 31.6 (d, C-6), 29.6 (t, C-3), 26.2 (t, C-4), 21.6 (q, CH_3); *m/z*:168 ($M^{+\cdot}$, 1), 124 (4), 111 (8), 96 (26), 95 (39), 83 (41), 82 (27), 81 (100), 68 (19), 67 (32), 55 (63); 98% e.e. (by chiral HRGC γ-CDX), $[\alpha]_D^{25} = +4.6$ (*c* 0.33, CH_3OH), $[\Theta]_{236} = +193$, $[\Theta]_{209} = -385$, $[\Theta]_{195} = -894$.

4.7.2. cis*-6-Methyl-octahydro-2*H*-1-benzopyran-2-one **6c** and* trans*-6-methyl-octahydro-2H-1-benzopyran-2-one **7c**[28]*

Since the mixture of lactones **4c**, **5c**, **6c** and **7c** could not be completely separated, only a few signals were identified in the ^1H and ^{13}C NMR spectra of **6c** and **7c**.

Compound **6c**: ^1H NMR, δ, ppm ($CDCl_3$+C_6D_6): 4.20 (1H, m, $W_H = 18.9$); ^{13}C NMR, δ, ppm: 80.0 (d), 20.5 (q).

Compound **7c**: ^1H NMR, δ, ppm ($CDCl_3$): 3.79 (1H, m); ^{13}C NMR, δ, ppm: 83.9 (d), 17.7 (q).

*4.8. Separation of the δ-lactones **4d** and **5d***

The 80:20 mixture of lactones **4d** and **5d** (0.7 g, 4.2 mmol), obtained from the reduction of the δ-keto ester **2d** with baker's yeast, was dissolved in methanol (20 ml), KOH (0.7 g, 12.6 mmol) and the mixture was stirred at room temperature for 72 h. Evaporation of methanol left an oil which was dissolved in anhydrous DMF (5 ml) and added of isopropylbromide (3.0 ml, 25.2 mmol). The mixture was then stirred at room temperature for 24 h. When the reaction was over, water (14 ml) was added and the mixture was extracted three times with ether. The combined organic extracts were washed with water and dried over Na_2SO_4. The crude reaction mixture (50% yield), containing the δ-hydroxy esters *cis*-**8** and *trans*-**8**, was separated by flash chromatography (eluant: light petroleum:ethyl acetate, gradient from 99:1 to 88:12) furnishing the δ-

hydroxy ester *cis*-**8** as a pure compound and a mixture of **4d**, **5d** and *trans*-**8** in the ratio of 17:17:66. Evidently, silica was acid enough as to recyclize, albeit partially, the δ-hydroxy esters. The δ-hydroxy ester *cis*-**8** and the mixture of products containing *trans*-**8** were lactonized separately in refluxing benzene with *p*-toluensulfonic acid as a catalyst for 30 min. The former reaction furnished (–)-**4d** as pure compound and the latter gave a 15:85 mixture of (–)-**4d** and (–)-**5d**.

*4.8.1. Methylethyl (1*S*,2*S*)-(–)-3-(2-hydroxycycloheptyl)propionate* cis-***8***

Oil; IR, cm^{-1} (film): 1730 (COO), 3460 (OH); ^1H NMR, δ, ppm: 5.01 (1H, sept, J = 6.4 Hz, C*H*$(CH_3)_2$), 3.91 (1H, bs, C*H*OH), 2.33 (2H, m), 1.87–1.35 (14H, m), 1.23 (6H, d, J = 6.4 Hz, CH_3); ^{13}C NMR, δ, ppm: 173.8 (s), 72.3 (d), 67.6 (d), 44.2 (d), 35.4 (t), 33.0 (t), 28.2 (t), 27.8 (t), 27.2 (t), 26.6 (t), 21.8 (2q), 21.8 (t); *m*/*z*: 168 (9), 150 (12), 112 (75), 111 (46), 108 (17), 98 (100), 97 (55), 96 (85), 95 (57), 94 (16), 93 (21), 84 (56), 83 (80), 82 (63), 81 (58), 80 (24), 79 (35), 77 (11), 70 (21), 69 (20), 68 (42), 67 (75), 66 (11), 57 (14), 56 (14), 55 (98), 54 (38), 53 (30); >99% e.e., $[\alpha]_D^{25} = -20.0$ (*c* 0.30, CH_3OH), $[\Theta]_{212} = -1665$.

4.8.2. Methylethyl trans-*3-(2-hydroxycycloheptyl)propionate* trans-***8***

^1H NMR, δ, ppm: 5.01 (1H, sept, J = 6.3 Hz, C*H*$(CH_3)_2$), 3.46 (1H, dt, $J_1 = J_2 = 7.4$ Hz, $J_3 = 3.7$ Hz, C*H*OH), 2.35 (2H, m), 1.87–1.35 (14H, m), 1.24 (6H, d, J = 6.3 Hz, CH_3); ^{13}C NMR, δ, ppm: 173.8 (s), 76.4 (d), 67.6 (d), 46.8 (d), 36.3 (t), 32.2 (t), 29.5 (t), 28.9 (t), 28.8 (t), 26.6 (t), 22.3 (t), 21.8 (2q).

*4.8.3. (4a*S*,9a*S*)-(–)-Octahydro-2(3*H*)-cyclohepta[*b*]pyran-2-one* ***4d***

IR, cm^{-1} (film): 1765 (C=O); ^1H NMR δ, ppm: 4.58 (1H, dt, $J_1 = J_2 = 4.6$ Hz, $J_3 = 8.9$ Hz, H-9a), 2.45 (2H, t, J = 6.8 Hz, H-3), 2.16 (3H, m), 1.80–1.62 (2H, m), 1.52–1.25 (4H, m); ^{13}C NMR, δ, ppm: 172.3 (s), 81.8 (d), 36.6 (d), 32.3 (t), 29.2 (t), 28.4 (t), 27.8 (t), 27.1 (t), 26.4 (t), 21.6 (t); *m*/*z*: 168 ($M^{+\cdot}$, 5%), 112 (40), 111 (24), 98 (54), 97 (34), 96 (48), 95 (35), 83 (56), 82 (46), 81 (42), 79 (25), 77 (10), 68 (38), 67 (67), 55 (100), 54 (43), 53 (28); >99% e.e. (by chiral HRGC γ-CDX), $[\alpha]_D^{25} = -41.7$ (*c* 0.24, CH_3OH), $[\Theta]_{212} = -3651$.

*4.8.4. (4a*R*,9a*S*)-(–)-Octahydro-2(3*H*)-cyclohepta[*b*]pyran-2-one* ***5d*** *(in admixture with 15% of (–)-****4d****)*

Only a few signals could be identified in the ^1H NMR spectrum, δ, ppm: 4.01 (1H, dt, $J_1 = J_2 = 9.3$, $J_3 = 5.2$ Hz, H-9a), 2.61 (1H, m), 2.48 (1H, m), 2.07 (1H, m), 1.90–1.25 (12H, m); ^{13}C NMR, δ, ppm: 171.9 (s, C=O), 85.8 (d), 40.1 (d), 34.0 (t), 30.1 (t), 29.0 (t), 27.5 (t), 26.3 (t), 25.3 (t), 21.5 (t); *m*/*z*: 168 ($M^{+\cdot}$, 4%), 112 (36), 111 (16), 98 (46), 97 (26), 96 (45), 95 (26), 93 (10), 84 (37), 83 (57), 81 (54), 80 (14), 79 (22), 70 (13), 69 (16), 68 (30), 67 (60), 56 (12), 55 (100), 54 (29), 53 (24); e.e. >99% (by chiral HRGC γ-CDX), $[\alpha]_D^{25} = -31.9$ (*c* 0.26, CH_3OH); $[\Theta]_{236} = +359$, $[\Theta]_{205} = -862$.

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