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Synthesis of optically active α-benzyl paraconic acids and their esters and assignment of their absolute configuration

Federico Berti, Cristina Forzato *, Giada Furlan, Patrizia Nitti, Giuliana Pitacco, Ennio Valentin *, Ennio Zangrando

Dipartimento di Scienze Chimiche, Università degli Studi di Trieste, via Licio Giorgieri 1, I-34127 Trieste, Italy

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ABSTRACT

The *cis*- and *trans*-4-benzylparaconic acids and their ethyl esters were synthesized with high enantiomeric excess by hydrolysis of the corresponding diastereomeric lactonic esters using α-chymotrypsin. Thus, at low conversion values, *cis*- and *trans*-4-benzyl-5-oxo-3-tetrahydrofurancarboxylic acids were separately isolated with 99% ee and 92% ee, respectively. Both ethyl ester diastereomers were also obtained in enantiopure form. The absolute configuration of the *trans*-lactonic acid was assigned by ^{1}H NMR analysis of its ester derivatives with both enantiomers of 1-(9-anthryl)-2,2,2-trifluoroethanol, while that of the *cis*-lactonic acid was assigned by means of X-ray analysis of a crystalline derivative. The circular dichroism curves of the products obtained are also reported.

1. Introduction

Compounds containing the γ-lactone ring are constantly synthesized because of their potential use as drugs in the pharmaceutical industry.[1] Some alkyl-substituted γ-butyrolactones, such as α-benzyl-α-methyl-γ-butyrolactone, have been shown to have both inhibitory and stimulatory effects on $GABA_A$ receptors.[2] The interest in the synthesis of enantiopure functionalized β-carboxylated γ-butyrolactones (generally called paraconic acid derivatives) is increasing, in view of their potential biological activity.[3] We recently focused our attention on the synthesis of optically active diastereomeric ethyl γ-benzylparaconates involving kinetic enzymatic resolution of their esters with α-chymotrypsin.[4] The absolute configurations of the enantiopure *cis*- and *trans*-γ-benzylparaconic acids were determined by means of a comparison of ^{1}H NMR spectra of their esters with (+)- and (−)-1-(9-anthryl)-2,2,2-trifluoroethanol.[5] Herein, we report the synthesis of their regioisomeric ethyl α-benzylparaconates in enantiopure form with the aim of verifying the effects of a change in the position of the benzyl group on the efficiency of the same hydrolytic enzyme.

2. Results and discussion

2.1. Synthesis of substrates

Racemic ethyl α-benzylparaconates **5a**,**b** were synthesized following the procedure as indicated in Scheme 1. Diethyl benzylmalonate and bromoacetate were reacted, using a slightly modified literature procedure,[6] generating the triester intermediate **1** which rearranged under strongly basic conditions to give compound **2**.[7] Reaction with paraformaldehyde in the presence of trace amounts of potassium hydrate at room temperature[8] furnished the α-benzyl-β,β-diethoxydicarbonyl-γ-lactone **3**. Hydrolysis and decarboxylation, under acidic conditions, gave a 3:7 diastereomeric mixture of the *cis*- and *trans*-lactonic acids **4a** and **4b**, which were esterified[9] to the target lactonic esters **5a** and **5b**, respectively.

The lactonic esters **5a** and **5b** were separated by column chromatography. The assignment of the *cis*/*trans* configuration was based on the ^{1}H NMR chemical shift values of H-3 and H-4. As reported in the literature[10] for a series of different analogues, in the *trans*-lactone, H-3 resonates at higher field than H-4, while the reverse is true for the *cis*-lactone (Fig. 1).

These assignments were then confirmed by DIFNOE experiments carried out on the *cis*-diastereomer **5a**. Irradiation of H-4 at 3.08 ppm clearly enhanced the signal of H-3 at 3.30 ppm, although the signal of H-3 was partially overlapped by one of the benzyl protons.

2.2. Enzymatic hydrolyses

Enzymatic hydrolyses were performed on the lactonic esters **5a** and **5b** using a series of commercially available enzymes, namely Porcine pancreatic lipase (PPL), Lipase from *Pseudomonas species* (PS), Lipase from *Pseudomonas fluorescens* (AK), *Candida cylindracea* lipase (CCL), *Aspergillus niger* (AP12), Lipase from *Candida rugosa* (AY), *Mucor miehei* lipase (MML), *Candida antarctica* lipase (CAL), Porcine liver acetone powder (PLAP), Horse liver acetone powder

* Corresponding authors. Tel.: +39 040 5583917; fax: +39 040 5583903 (E.V.).
E-mail address: evalentin@units.it (E. Valentin).

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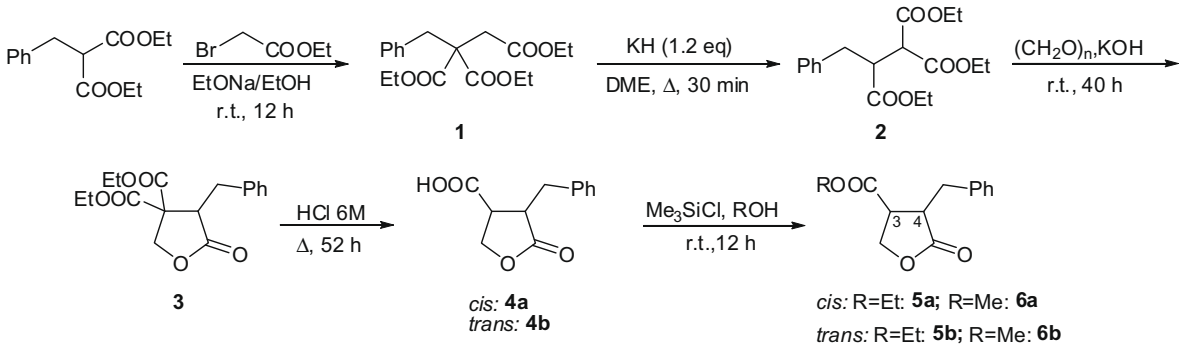


Scheme 1. Synthesis of racemic substrates **5a** and **5b**.

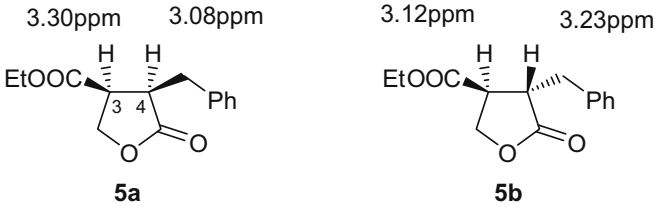


Figure 1. Chemical shifts of H-3 and H-4 for lactones **5a** and **5b**.

(HLAP), α-chymotrypsin (α-CT) and proteases from *Bacillus subtilis* (SUB). Hydrolyses were monitored by a pH-STAT instrument with the continuous addition of 1 M NaOH. Since the molecules presented two possible sites of attack by the enzyme, namely the ethoxycarbonyl group and the lactone group, attention was paid to the regioselective enzymes, which were effective in hydrolysing the ethoxycarbonyl group exclusively. Tables 1 and 2 list only the results obtained with those enzymes which proved to be regioselective.

The *cis*-diastereomer **5a** was a good substrate for both α-chymotrypsin (α-CT) and PPL, whose enantiomeric ratios *E*'s were higher than 200 (Table 1, entries 1 and 2). As a consequence, the resulting *cis*-lactonic acid (−)-(3*S*,4*R*)-**4a** was isolated in enantiopure form. In spite of its very low *E*-value, PLAP is interesting because it proved to be enantiocomplementary with respect to α-CT and PPL. Of the other enzymes checked, HLAP was not regioselective, leading to the ester (+)-(3*R*,4*S*)-**5a** with 83% ee, formed by ring fission and ring closure reactions, together with the lactonic acid (−)-(3*S*,4*R*)-**4a** with 55% ee. The same behaviour, albeit with lower enantioselectivity, was observed for Lipase PS, while the other enzymes proved to be uneffective.

On the contrary, for the *trans*-diastereomer **5b**, the hydrolysis had fairly high enantioselectivity only with α-chymotrypsin, whose enantiomeric ratio *E*, however, was not so high as for its diastereomer **5a**. The *trans*-lactonic acid **4b** was therefore isolated with 92% ee. Also CCL, Lipase AY, MML and CAL (Table 2, entries 2–5,) were completely regioselective affording the corresponding lactonic acid **4b**, however, with low enantioselectivity. The other enzymes checked did not hydrolyse the substrate.

Enzymatic hydrolyses carried out with acetone as a cosolvent, which had been successful for the γ-benzylparaconate analogues,[4] proved to be ineffective.

The lactonic esters (+)-**5a** and (+)-**5b** were obtained in 94% ee and 96% ee, respectively, by hydrolysis with α-CT of the corresponding lactonic esters recovered from the previous reactions (see Section 4).

2.3. Determination of the absolute configuration of the products

2.3.1. NMR analysis of derivatives 7 and 8

In our previous work, we assigned the absolute configuration of γ-benzylparaconic acids,[4] using a slightly modified method proposed by Riguera[13] for linear carboxylic acids. In accordance with this method, the acid is transformed into a pair of diastereomeric esters by reaction with the two enantiomers of 1-(9-anthryl)-2,2,2-trifluoroethanol. The shielding due to the anthryl diamagnetic anisotropy on the protons of the molecule is then evaluated by ^{1}H NMR. The absolute configuration of the molecule is deduced from the difference in chemical shift ($\Delta\delta^{R,S}$) between the two diastereomers of the protons contained in the substituents L_1 and L_2, linked to the stereocentre (Fig. 2).

In the original Riguera's model, the minimum energy conformation of the esters was assumed to be that shown in Figure 2, that is, with the protons of the two stereocentres in an *anti*-conformation. To make sure that the methodology was also applicable to our systems, a conformational study was performed on the two diastereomers **7** and **8**, which are obtained by esterification of the *trans*-α-benzylparaconic acid (−)-**4b** with (+)- and (−)-1-(9-anthryl)-2,2,2-trifluoroethanol (Scheme 2).

Table 1
Enzymatic hydrolyses[a] of compound **5a**

Entry	Enzyme	*E*[b]	Conv.[c]	Time (h)	Lactonic acid **4a**			Unreacted ester **5a**		
					Sign of α	ee[d] (%)	Abs Config.	Sign of α	ee[e] (%)	Abs Config.
1	α-CT	>200	12	5.7	(−)	>99	(3*S*,4*R*)	(+)	13	(3*R*,4*S*)
2	PPL	>200	7	33	(−)	>99	(3*S*,4*R*)	(+)	7	(3*R*,4*S*)
3	PLAP	3	31	5.2	(+)	41	(3*R*,4*S*)	(−)	18	(3*S*,4*R*)

[a] Reaction conditions: phosphate buffer, pH 7.4, rt.

[b] *E*-values $\left(E=\frac{\ln\frac{[ee_P(1-ee_S)]}{[ee_P+ee_S]}}{\ln\frac{[ee_P(1+ee_S)]}{[ee_P+ee_S]}}\right)$ were calculated from the formula containing the enantiomeric excesses of both the substrate and the product.[11]

[c] Calculated.[12]

[d] Determined by chiral HRGC on the methyl ester derivative **6a**.

[e] Determined by chiral HRGC.

Table 2
Enzymatic hydrolyses[a] of compound **5b**

Entry	Enzyme	E[b]	Conv.[c]	Time (h)	Lactonic acid **4b**			Unreacted ester **5b**		
					Sign of α	ee[d] (%)	Abs Config.	Sign of α	ee[e] (%)	Abs Config.
1	α-CT	29	18	0.9	(−)	92	(3*S*,4*S*)	(+)	20	(3*R*,4*R*)
2	CCL	2	31	1.3	(−)	33	(3*S*,4*S*)	(+)	15	(3*R*,4*R*)
3	Lipase AY	2	27	8.7	(−)	24	(3*S*,4*S*)	(+)	9	(3*R*,4*R*)
4	MML	5	17	1.2	(−)	60	(3*S*,4*S*)	(+)	12	(3*R*,4*R*)
5	CAL	9	17	2.6	(−)	77	(3*S*,4*S*)	(+)	16	(3*R*,4*R*)

[a] Reaction conditions: phosphate buffer, pH 7.4, rt.
[b] E-values $\left(E=\frac{\ln\frac{[ee_P(1-ee_S)]}{[ee_P+ee_S]}}{\ln\frac{[ee_P(1+ee_S)]}{[ee_P+ee_S]}}\right)$ were calculated from the formula containing the enantiomeric excesses of both the substrate and the product.[11]
[c] Calculated.[12]
[d] Determined by chiral HRGC on the methyl ester derivative **6b**.
[e] Determined by chiral HRGC.

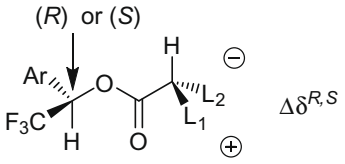
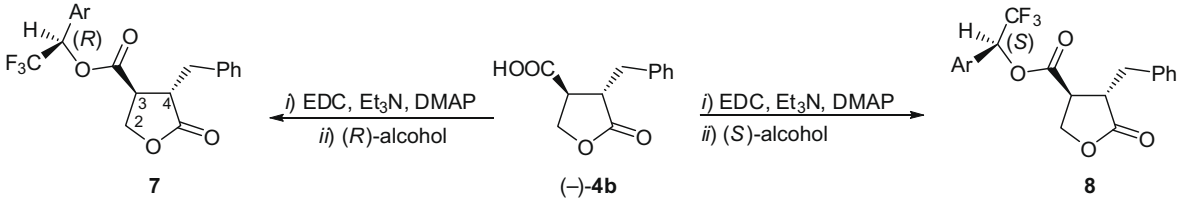


Figure 2. Riguera's model.

The two diastereomeric esters **7** and **8** have been submitted to an extensive conformational search, which is carried out with a Monte Carlo algorithm operating on PM3 geometry optimizations.[14] We have found four and five different energy minima for esters **7** and **8**, respectively, and their structural parameters are reported in Table 3, together with their enthalpy data.

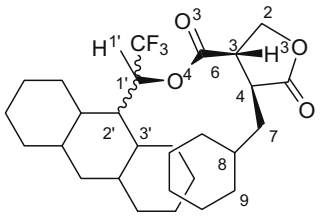
The ground state conformations of ester **8** correspond to those supposed by the Riguera's model; however, the ground state conformation of ester **7** is very different, since oxygen 3 and hydrogen 3 are found in an *anti*-conformation. For this reason, the shielding effect of the anthryl system is predicted to operate on the same side of the molecule (namely on C4 and C7) in both esters. This can be clearly seen from the superimposition reported in Figure 3: in both esters, the C4-benzyl region of the molecules lies in the cone of diamagnetic anisotropy (hemiangle 45° from the centre of the anthryl system), while the protons at C2 are not influenced by this effect.

The chemical shifts of the protons on C-2 and C-4 of the lactone ring, as well as those of the benzylic protons in diastereomers **7** and **8**, are reported in Table 4. The stereocentre of the alcoholic component is indicated as **1′**.



Scheme 2. Synthesis of compounds **7** and **8** from (−)-**4b**.

Table 3
PM3 conformation analysis of esters **7** and **8**: structures, energies and predicted shielding effects



Compound	Conf.	$C_3'C_2'C_1'H_1'$	$H_1'C_1'O_4C_6$	$C_1'O_4C_6O_3$	$O_3C_6C_3C_2$	$C_3C_4C_7C_8$	$C_4C_7C_8C_9$	ΔH_f rel (absolute) (Kcal/mol)	Population (%)	Shielding on C_2	Shielding on C_4–C_7
7	0	181.8	0.4	357.6	254.2	72.3	277.7	0 (−224.22)	99.99	No	Yes
	1	176.5	198.0	19.6	243.1	71.3	256.3	7.69	—	Yes	No
	2	185.8	205.6	15.2	55.7	160.4	100.0	7.75	—	No	Yes
	3	177.5	199.0	19.5	240.3	162.6	109.9	8.80	—	Yes	No
8	0	182.7	5.5	356.7	64.0	73.1	77.8	0 (−224.30)	61.7	No	Yes
	1	182.3	4.9	358.6	252.8	72.9	76.9	0.51	26	Yes	No
	2	181.0	5.2	4.4	69.4	172.0	109.5	1.08	10	No	Yes
	3	180.6	4.8	182.9	75.6	169.0	289.3	2.06	1.9	No	No
	4	211.8	181.5	350.4	239.2	74.3	256.3	7.22	0.4	No	Yes

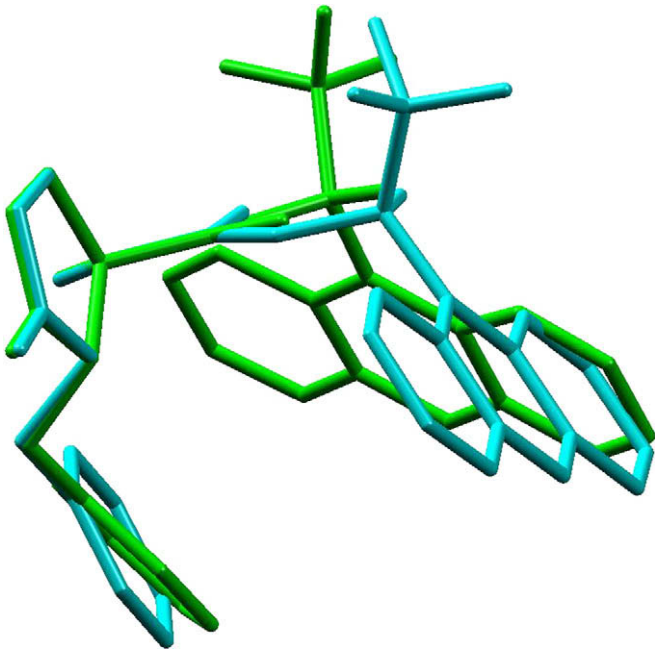


Figure 3. Overlay of the ground state conformations of esters **7** (blue) and **8** (green).

Table 4
Selected chemical shift values for compounds **7** and **8**

	H-2	$\Delta\delta^{R,S}$	H-4	$\Delta\delta^{R,S}$	CH_2Ph	$\Delta\delta^{R,S}$
(1′*R*,3*S*,4*S*)-**7**	4.11[a]	−0.14	3.21	+0.04	3.14[a]	+0.16
(1′*S*,3*S*,4*S*)-**8**	4.25[a]		3.17		2.98[a]	

[a] Average chemical shift of the two geminal protons (see Section 4).

The observed difference in chemical shifts can be explained on the basis of the very different population of the other conformation available for the two compounds. In ester **7,** the ground state conformation is also the only one to be populated at room temperature, while the conformations of ester **8** are very close in energy, and over 25% of the molecules populate conformation **1**, where the shielding operates on C2 (Fig. 4).

For this reason, shielding on the C4 side of the molecules is less significant in compound **8**. This allows us to predict the values of $\Delta\delta^{R,S}$ in qualitative accordance with the experimental data, and thus determines the absolute configuration of compound (−)-**4b** to be (3*S*,4*S*).

It was not possible to apply the same method to the *cis*-α-benzylparaconic acid (−)-**4a** because it did not react with either enantiomer of 1-(9-anthryl)-2,2,2-trifluoroethanol, although many attempts have been made also by changing the reaction conditions.

2.3.2. X-ray analysis of (−)-9

The assignment of the (3*S*,4*R*) absolute configuration to the *cis*-isomer (−)-**4a** was accomplished by means of X-ray analysis of the ester (−)-**9**, which is obtained from the reaction of (−)-**4a** with 2,4′-dibromoacetophenone under basic conditions (Scheme 3).

Single crystal structural analysis reveals in the unit cell the presence of two independent molecules having a different conformation about the O–C ester bond (C(9)–O(2)–C(8)–C(7) torsion angle of 134.6(5)°, see Fig. 5, and of 77.7(5)° in the other molecule). The lactone ring presents an 'envelope' conformation with carbon C(10) slightly displaced by 0.53(1) Å (0.55(1) Å in the other species) from the coplanar O(4)/C(11)/C(12)/C(13) atoms. The two independent molecules in the crystal packing interact through weak π–π stacking Br–phenyl rings (distance between centroid rings 3.860(4) Å).

2.3.3. CD analysis

Since both lactonic acids (−)-**4a** and (−)-**4b** were substituted at the α-position, we analyzed their circular dichroism spectra in order to verify whether the empirical rules[15] formulated for the assignment of the absolute configuration to γ-lactones were valid. Among these rules, the Okuda rule[16] found its applicability to α-substituted γ-lactones. The Okuda rule was originally assessed for α-hydroxy-γ-lactones, but its validity was further extended to α-alkyl-γ-lactones.[17] In accordance with this rule, the sign of the Cotton effect associated with the $n\rightarrow\pi^*$ transition of the lactone group is strictly dependent on the absolute configuration of C-α. Since the CD curves of the lactones (−)-**4a** and (−)-**4b** are opposite (Fig. 6), the two lactones must have opposite absolute configurations at C-α. The corresponding esters (+)-**5a** and (+)-**5b** also have opposite Cotton effect, and hence they have opposite configuration

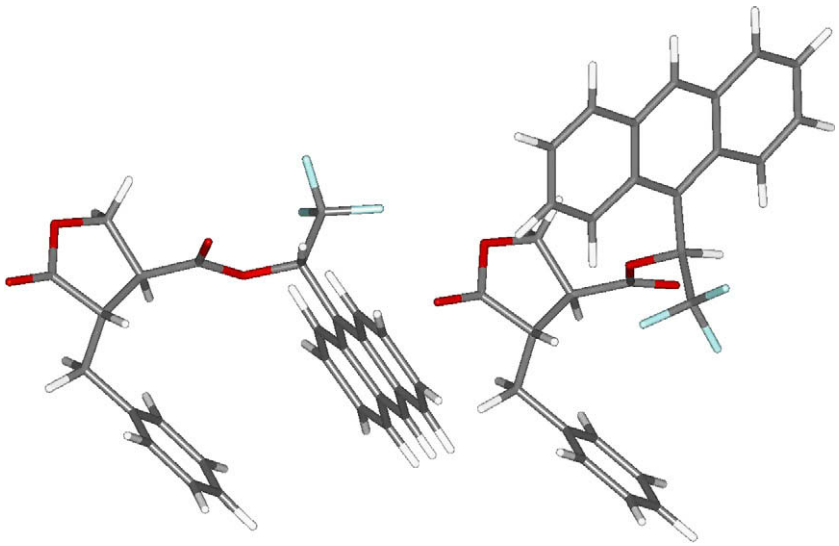
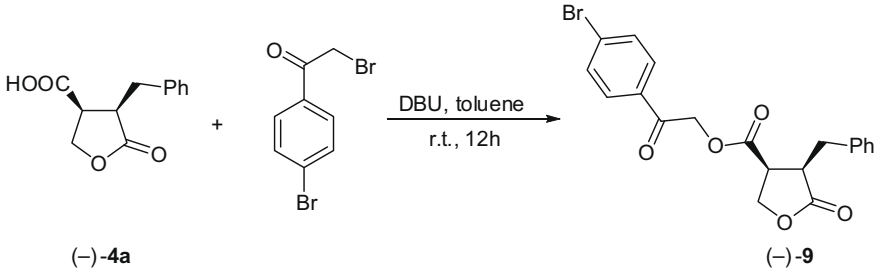


Figure 4. Conformations 0 (left) and 1 (right) of ester **8**.



Scheme 3. Synthesis of the ester (–)-**9**.

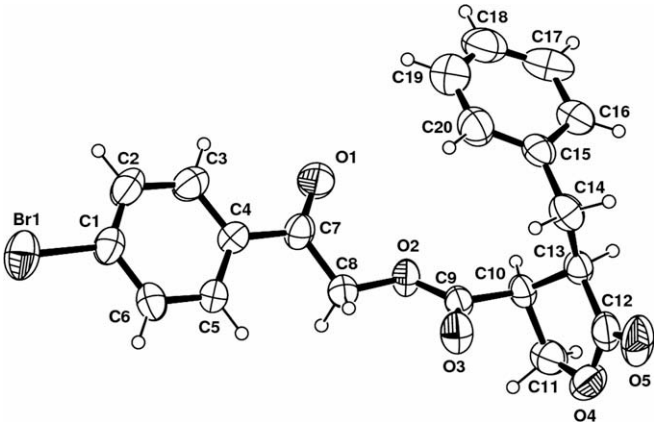


Figure 5. ORTEP diagram of one of the two independent molecules of **9**.

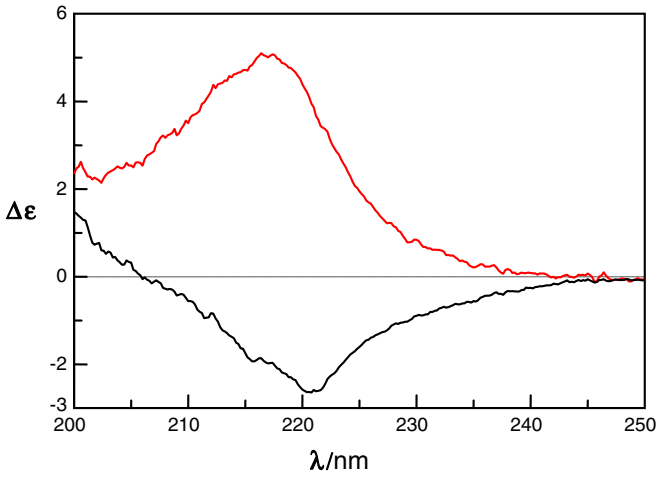


Figure 7. CD spectra of lactones (+)-**5a** (red) and (+)-**5b**.

(Fig. 7). As a consequence, the validity of the Okuda rule is confirmed.

3. Conclusions

The *cis*- and *trans* α-benzylparaconates **5a** and **5b** were successfully resolved by α-Chymotrypsin (α-CT), which has already proven to be particularly suitable for kinetic resolution of *N*-benzyl γ-lactamic esters[18] and *cis*- and *trans*-γ-benzylparaconates,[4] thus suggesting that the presence of a benzyl group on either a lactone ring or a lactam ring is important for a favourable interaction with the enzyme, independent of the position of the group. Furthermore, this work demonstrates that the joint use of different methodologies is sometimes necessary to arrive at the correct assignment of the absolute configuration.

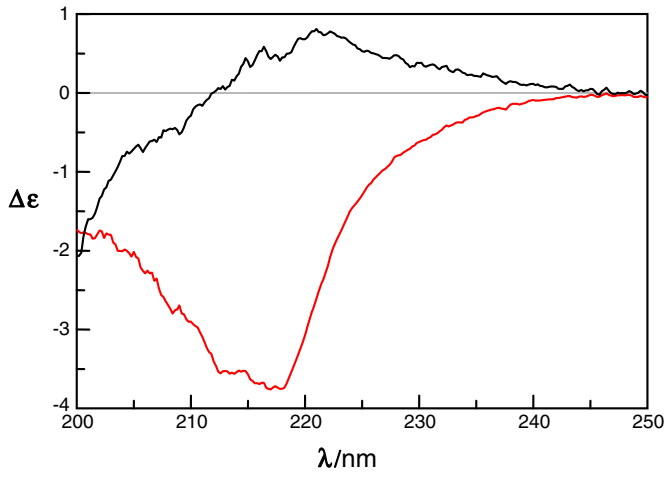


Figure 6. CD spectra of lactones (–)-**4a** (red) and (–)-**4b**.

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, 100 MHz for carbon) and on a Jeol EX-270 spectrometer (270 MHz for proton, 68 MHz for carbon) using deuteriochloroform as a solvent and tetramethylsilane as the internal standard. Coupling constants are given in Hertz. Optical rotations were determined on a Perkin Elmer Model 241 polarimeter; $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. CD spectra were obtained on a Jasco J-710 spectropolarimeter (0.1 cm cell); $\Delta\varepsilon$ values are given in cm^2 mmol^{-1}. UV spectra were recorded on a UNICAM HeλIOS β spectrophotometer; ε values are given in dm^3 mol^{-1} cm^{-1}. Capillary gas chromatographic measurements were performed on a Carlo Erba GC 8000 instrument and on a Shimadzu GC-14B instrument, equipped with a flame ionization detector, the capillary columns being OV 1701 (25 m × 0.32 mm) (carrier gas He, 40 KPa, split 1:50) and a Chiraldex™ type G-TA, trifluoroacetyl γ-cyclodextrin (40 m × 0.25 mm) (carrier gas He, 180 KPa, split 1:100) or DiMePe β-cyclodextrin (25 m × 0.25 mm) (carrier gas He, 110 KPa, split 1:50). Enzymatic hydrolyses were performed using a pH-stat Controller PHM290 Radiometer Copenhagen. Mass spectra were recorded on an ion trap instrument Finningan GCQ (70 eV). HRMS spectra were performed on a Finnigan MAT95XP spectrometer. 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 bp 40–70 °C, and ether to diethyl ether. Commercial grade solvents were used without further purification. Diethyl benzylmalonate, ethyl bromoacetate, (+) and (−)-1-(9-anthryl)-2,2,2-trifluoroethanol were commercial products.

4.2. Synthesis of racemic substrates

4.2.1. 3-Phenyl-1,2,2-propanetricarboxylic acid 1,2,2-triethyl ester 1[7]

To a solution of 150 mmol of EtONa in EtOH (3.45 g of Na in 85 mL of absolute ethanol), 23.3 mL (100 mmol) of diethyl benzylmalonate and 13.3 mL (120 mmol) of ethyl bromoacetate were added. The mixture was stirred for 12 h under an argon atmosphere. After evaporation of the solvent, 3 N H_2SO_4 was added, and the mixture was extracted with ether and the organic phase dried on anhydrous Na_2SO_4. After evaporation of the solvent, compound **1** was obtained as a colourless oil (33.0 g, 98%). ν_{max}(film)/cm^{-1} 1736 (COO), 1171 (C–O–C); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.25 (3H, m, Ph), 7.09 (2H, m, Ph), 4.22 (2H, q, *J* 7.1, O*CH*$_2$CH$_3$), 4.21 (2H, q, *J* 7.1, O*CH*$_2$CH$_3$), 4.16 (2H, q, *J* 7.1, O*CH*$_2$CH$_3$), 3.39 (2H, s, C*H*$_2$Ph), 2.85 (2H, s, C*H*$_2$COOEt), 1.27 (3H, t, *J* 7.1, C*H*$_3$CH$_2$O), 1.26 (6H, t, *J* 7.1, C*H*$_3$CH$_2$O); ^{13}C NMR (100 MHz; $CDCl_3$) δ 171.1 (s, *C*OOEt), 170.0 (s, *C*OOEt), 169.9 (s, *C*OOEt), 135.8 (s, Ph), 130.1 (2 × d, Ph), 128.4 (2 × d, Ph), 127.2 (d, Ph), 61.8 (t, O*CH*$_2$CH$_3$), 61.7 (t, O*CH*$_2$CH$_3$), 60.8 (t, O*CH*$_2$CH$_3$), 55.9 (s, *C*(COOEt)$_2$), 38.6 (t, *C*H$_2$Ph), 36.8 (t, *C*H$_2$COOEt), 14.1 (q, *C*H$_3$CH$_2$O), 14.0 (q, *C*H$_3$CH$_2$O), 13.9 (q, *C*H$_3$CH$_2$O).

4.2.2. 3-Phenyl-1,1,2-propanetricarboxylic acid 1,1,2-triethyl ester 2[7]

To a suspension of 18.0 g of KH (30% KH in mineral oil washed with petroleum ether), 150 mL of 1,2-dimethoxyethane was added. A solution of 33.0 g (98.1 mmol) of compound **1** in 150 mL of 1,2-dimethoxyethane was added dropwise to the mixture, and the resulting mixture was refluxed for 30 min. At the end of the reaction, 20 mL of cool water was added and 4 M HCl until neutralization. The mixture was extracted with ether, and the organic phase was washed with $NaHCO_3$ saturated solution, water and brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave compound **2** as an oil (30.7 g, 93%); ν_{max}(film)/cm^{-1} 1736 (COO), 1171 (C–O–C); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.40–7.00 (5H, m, Ph), 4.18 (4H, q, *J* 7.1, 2 O*CH*$_2$CH$_3$), 4.05 (2H, q, *J* 7.1, O*CH*$_2$CH$_3$), 3.70 (1H, d, *J* 9.2, C*H*(COOEt)$_2$), 3.40 (1H, dt, $J_{2,3}$ 7.3, $J_{1,2}$ 9.2, C*H*CH$_2$Ph), 2.93 (2H, d, *J* 7.3, C*H*$_2$Ph), 1.28 (3H, t, *J* 7.1, C*H*$_3$CH$_2$O), 1.24 (3H, t, *J* 7.1, C*H*$_3$CH$_2$O), 1.08 (3H, t, *J* 7.1, C*H*$_3$CH$_2$O); ^{13}C NMR (100 MHz; $CDCl_3$) δ 172.6 (s, *C*OOEt), 167.8 (s, *C*OOEt), 167.5 (s, *C*OOEt), 137.6 (s, Ph), 129.0 (2 × d, Ph), 128.4 (2 × d, Ph), 126.6 (d, Ph), 61.6 (t, O*CH*$_2$CH$_3$), 61.5 (t, O*CH*$_2$CH$_3$), 60.6 (t, O*CH*$_2$CH$_3$), 53.4 (d, *C*H(COOEt)$_2$), 46.4 (d, *C*HCOOEt), 36.0 (t, *C*H$_2$Ph), 13.9 (q, *C*H$_3$CH$_2$O), 13.8 (q, *C*H$_3$CH$_2$O), 13.7 (q, *C*H$_3$CH$_2$O).

4.2.3. Diethyl 4-benzyl-5-oxo-3,3-tetrahydrofurandicarboxylate 3

At first, 3.50 g (2.5 equiv) of paraformaldehyde (polyoxymethylene) and 72 mg (1.3 mmol) of KOH were added to compound **2** (15.74 g, 46.8 mmol).[8] The mixture was stirred for 40 h at rt. At the end of the reaction, the mixture was filtered and washed with $CHCl_3$. Evaporation of the solvent gave compound **3** as a colourless oil (14.92 g, 99%); ν_{max}(film)/cm^{-1} 1789 (O–C=O), 1735 (COO); ^{1}H NMR (270 MHz; $CDCl_3$) δ 7.31–7.20 (5H, m, Ph), 4.62 (1H, d, *J* 9.9, *H*-2), 4.38 (1H, d, *J* 9.9, *H*-2), 4.23 (1H, q, *J* 7.2, O*CH*$_2$CH$_3$), 4.20 (1H, q, *J* 7.2, O*CH*$_2$CH$_3$), 4.08 (1H, q, *J* 7.2, O*CH*$_2$CH$_3$), 4.04 (1H, q, *J* 7.2, O*CH*$_2$CH$_3$), 3.49 (1H, t, X part of an ABX system, J_{AX} 6.9, J_{BX} 6.3, *H*-4), 3.08 (1H, A part of an ABX system, J_{AB} 14.2, J_{AX} 6.9, C*H*Ph), 3.04 (1H, B part of an ABX system, J_{AB} 14.2, J_{BX} 6.3, C*H*Ph), 1.26 (3H, t, *J* 7.2, C*H*$_3$CH$_2$O), 1.23 (3H, t, *J* 7.2, C*H*$_3$CH$_2$O); ^{13}C NMR (68 MHz; $CDCl_3$) δ 175.0 (s, *C*-5), 168.0 (s, *C*OOEt), 167.2 (s, *C*OOEt), 137.6 (s, Ph), 129.0 (2 × d, Ph), 128.2 (2 × d, Ph), 126.6 (d, Ph), 69.3 (t, *C*-2), 62.4 (t, O*CH*$_2$CH$_3$), 62.2 (t, O*CH*$_2$CH$_3$), 59.8 (s, *C*-3), 46.4 (d, *C*-4), 32.3 (t, *C*H$_2$Ph), 13.6 (q, *C*H$_3$CH$_2$O), 13.5 (q, *C*H$_3$CH$_2$O).

4.2.4. Ethyl 4-benzyl-5-oxo-3-tetrahydrofurancarboxylate 5a,b[19]

Compound **3** (8.0 g, 25 mmol) in 150 mL of 20% HCl was refluxed for 52 h. After evaporation of the solvent, a mixture of diastereomeric acids **4a**,**b**, in the ratio of 28:72 (^{1}H NMR), was obtained as a white solid (5.24 g, 95%). Their esterification was carried out in 120 mL of anhydrous ethanol, with 6.6 mL (52.4 mmol) of trimethylsilyl chloride added[9] under an Ar atmosphere and stirred for 12 h. Evaporation of the solvent left a 28:72 mixture of **5a** and **5b**, respectively (5.38 g, 91%).

Separation of the crude reaction mixture by flash chromatography (petroleum ether and ethyl acetate in 4:1 ratio) furnished **5a** (0.75 g, 13%) and **5b** (2.17 g, 37%) as oils. **5a**: ν_{max}(film)/cm^{-1} 1776 (O–C=O), 1732 (COO), 744–698; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.33–7.20 (5H, m, Ph), 4.38 (1H, dd, J_1 2.9, J_2 9.5, *H*-2), 4.28 (1H, dd, J_1 6.2, J_2 9.5, *H*-2), 4.18 (1H, q, *J* 7.1, O*CH*$_2$CH$_3$), 4.13 (1H, q, *J* 7.1, O*CH*$_2$CH$_3$), 3.30 (1H, m, *H*-3), 3.29 (1H, dd, J_1 4.5, J_2 14.5, C*H*Ph), 3.08 (1H, ddd, J_1 4.5, J_2 8.3, J_3 10.0, *H*-4), 2.83 (1H, dd, J_1 10.0, J_2 14.5, C*H*Ph), 1.24 (3H, t, *J* 7.1, C*H*$_3$CH$_2$O); ^{13}C NMR (100 MHz; $CDCl_3$) δ 176.1 (s, *C*-5), 170.6 (s, *C*OOEt), 138.0 (s, Ph), 128.7 (2 × d, Ph), 128.6 (2 × d, Ph), 126.8 (d, Ph), 67.7 (t, *C*-2), 61.4 (t, O*CH*$_2$CH$_3$), 44.0 (d, *C*-3), 44.0 (d, *C*-4), 32.2 (t, *C*H$_2$Ph), 14.0 (q, *C*H$_3$); *m*/*z* (EI, 70 eV): 248 (M$^{+\cdot}$, 20), 220 (18), 191 (13), 190 (100), 175 (23), 157 (6), 148 (33), 147 (48), 144 (14), 131 (31), 129 (18), 117 (10), 116 (6), 115 (15), 104 (7), 103 (7), 92 (7), 91 (74), 65 (13), 29 (7); *HRMS* (EI, 70 eV): calculated for $C_{14}H_{16}O_4$ (M$^{+\cdot}$) 248.1049, experimental 248.1049; *HRGC* (β-CDX): t_R = 238.7 min for the (+)-(3*R*,4*S*) enantiomer and t_R = 250.2 min for the (−)-(3*S*,4*R*) enantiomer (150 °C isotherm); *HRGC* (γ-CDX): t_R = 222.6 min for the (−)-(3*S*,4*R*) enantiomer and t_R = 231.7 min for the (+)-(3*R*,4*S*) enantiomer (150 °C isotherm). **5b**: ν_{max}(film)/cm^{-1} 1776 (O–C=O), 1732 (COO), 758–698; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.32–7.19 (5H, m, Ph), 4.28 (1H, t, *J* 8.8, *H*-2), 4.21 (1H, dd, J_1 8.8, J_2 9.1, *H*-2), 4.04 (1H, q, *J* 7.1, O*CH*$_2$CH$_3$), 4.01 (1H, q, *J* 7.1, O*CH*$_2$CH$_3$), 3.24 (1H, dd, J_1 6.4, J_2 9.7, C*H*Ph), 3.23 (1H, m, *H*-4), 3.12 (1H, dt, J_1 8.8, J_2 9.1, *H*-3), 3.03 (1H, dd, J_1 6.4, J_2 13.7, C*H*Ph), 1.18 (3H, t, *J* 7.1, C*H*$_3$CH$_2$O); ^{13}C NMR (100 MHz; $CDCl_3$) δ 176.4 (s, *C*-5), 170.7 (s, *C*OOEt), 136.7 (s, Ph), 129.4 (2 × d, Ph), 128.6 (2 × d, Ph), 127.0 (d, Ph), 67.2 (t, *C*-2), 61.6 (t, O*CH*$_2$CH$_3$), 44.6 (d, *C*-3), 44.4 (d, *C*-4), 34.7 (t, *C*H$_2$Ph), 13.9 (q, *C*H$_3$); *m*/*z* (EI, 70 eV): 248 (M$^{+\cdot}$, 35), 220 (10), 203 (16), 191 (12), 190 (91), 176 (12), 175 (100), 157 (10), 148 (39), 147 (63), 144 (11), 131 (26), 129 (26), 117 (10), 115 (16), 104 (6), 92 (10), 91 (98), 65 (15), 29 (9); *HRMS* (EI, 70 eV): calculated for $C_{14}H_{16}O_4$ (M$^{+\cdot}$) 248.1049, experimental 248.1046; *HRGC* (β-CDX): t_R = 138.7 min for the (+)-(3*R*,4*R*) enantiomer and t_R = 140.5 min for the (−)-(3*S*,4*S*) (150 °C isotherm); *HRGC* (γ-CDX): t_R = 116.0 min for the (−)-(3*S*,4*S*) enantiomer and t_R = 123.6 min for the (+)-(3*R*,4*R*) enantiomer (150 °C isotherm).

4.2.5. *cis*-4-Benzyl-5-oxo-3-tetrahydrofurancarboxylic acid 4a

Compound **5a** (60 mg, 0.24 mmol) was hydrolyzed in 5 mL of 6 M HCl at reflux for 2 h. White solid, mp 125–127 °C; ν_{max}(film)/cm^{-1} 3000, 1761, 1685, 744–698; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.30–7.20 (5H, m, Ph), 4.44 (1H, dd, J_1 2.6, J_2 9.5, *H*-2), 4.31 (1H, dd, J_1 4.8, J_2 9.5, *H*-2), 3.35 (1H, dd, J_1 8.0, J_2 14.3, C*H*Ph), 3.35 (1H, m, *H*-3), 3.10 (1H, ddd, J_1 4.6, J_2 8.0, J_3 9.6, *H*-4), 2.92 (1H, dd, J_1 9.6, J_2 14.3, C*H*Ph); δ_H (400 MHz; D_2O) 7.25–7.14 (5H, m, Ph), 4.35 (1H, dd, J_1 2.2, J_2 9.8, *H*-2), 4.28 (1H, dd, J_1 6.0, J_2 9.8, *H*-2), 3.36 (1H, ddd, J_1 5.7, J_2 8.2, J_3 9.8, *H*-4), 3.21 (1H, ddd, J_1 2.2, J_2 6.0, J_3 8.2, *H*-3), 3.08 (1H, dd, J_1 5.7, J_2 14.6, C*H*Ph), 2.66 (1H, dd, J_1 9.8, J_2 14.6, C*H*Ph); ^{13}C NMR (100 MHz; $CDCl_3$) δ 176.6 (s, *C*-5), 175.7 (s, *C*OOH), 137.7 (s, Ph), 129.4 (2 × d, Ph), 128.6

(2 × d, Ph), 126.8 (d, Ph), 67.7 (t, *C*-2), 44.0 (d, *C*-4), 43.7 (d, *C*-3), 31.9 (t, *C*H_2Ph); δ_C (68 MHz; D_2O) 180.8 (s, *C*-5), 175.8 (s, *C*OOH), 138.3 (s, Ph), 129.2 (2 × d, Ph), 129.1 (2 × d, Ph), 127.3 (d, Ph), 69.6 (t, *C*-2), 44.6 (d, *C*-4), 43.7 (d, *C*-3), 31.9 (t, *C*H_2Ph); *m*/*z* (EI, 70 eV) 220 ($M^{+\cdot}$, 22), 192 (20), 175 (9), 162 (19), 148 (50), 147 (60), 131 (26), 130 (11), 129 (14), 117 (4), 115 (14), 104 (11), 103 (9), 92 (17), 91 (100), 77 (8), 69 (13), 65 (18), 51 (8), 39 (8); *HRMS* (EI, 70 eV) calculated for $C_{12}H_{12}O_4$ ($M^{+\cdot}$) 220.0736, experimental 220.0738.

4.2.6. *trans*-4-Benzyl-5-oxo-3-tetrahydrofurancarboxylic acid 4b

Compound **5b** (420 mg, 1.70 mmol) was hydrolyzed in 14 mL of 6 M HCl at reflux for 2 h. White solid, mp 100–101 °C; ν_{max}(film)/cm^{-1} 3000, 1748, 1727, 758–683; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.61 (1H, br s, O*H*), 7.32–7.22 (5H, m, Ph), 4.26 (2H, d, *J* 8.4, *H*-2), 3.26 (1H, dt, J_1 5.8, J_2 9.5, *H*-4), 3.19 (1H, t, *J* 8.4, *H*-3), 3.16 (2H, d, *J* 5.8, CH_2Ph); ^{1}H NMR (400 MHz; D_2O) δ 7.24–7.15 (5H, m, Ph), 4.30 (1H, dd, J_1=8.4, J_2=9.2, *H*-2), 4.18 (1H, dd, J_1 8.1, J_2 9.2, *H*-2), 3.28 (1H, ddd, J_1 5.7, J_2 7.7, J_3 9.0, *H*-4), 3.19 (1H, app. t, *J* 8.4, *H*-3), 3.06 (1H, dd, J_1 5.7, J_2 14.0, C*H*Ph), 2.84 (1H, dd, J_1 7.7, J_2 14.0, C*H*Ph); ^{13}C NMR (100 MHz; $CDCl_3$) δ 176.9 (s, *C*-5), 175.5 (s, *C*OOH), 136.2 (s, Ph), 129.4 (2 × d, Ph), 128.6 (2 × d, Ph), 127.0 (d, Ph), 66.9 (t, *C*-2), 44.1 (d, *C*-4), 43.5 (d, *C*-3), 34.1 (t, *C*H_2Ph); *m*/*z* (EI, 70 eV): 220 ($M^{+\cdot}$, 32), 175 (24), 162 (12), 148 (60), 147 (77), 131 (25), 129 (20), 115 (19), 104 (7), 103 (7), 92 (13), 91 (100), 77 (12), 69 (15), 65 (24), 51 (12), 41 (13), 39 (14), 32 (10), 28 (27); *HRMS* (EI, 70 eV): calculated for $C_{12}H_{12}O_4$ ($M^{+\cdot}$) 220.0736, experimental 220.0736.

4.2.7. Methyl *cis*-4-benzyl-5-oxo-3-tetrahydrofurancarboxylate 6a

Esterification of acid **4a** with diazomethane furnished **6a** as an oil. ν_{max}(film)/cm^{-1} 1776, 1732, 698; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.33–7.13 (5H, m, Ph), 4.38 (1H, dd, J_1 3.3, J_2 9.5, *H*-2), 4.29 (1H, dd, J_1 6.3, J_2 9.5, *H*-2), 3.69 (3H, s, O*C*H_3), 3.34 (1H, ddd, J_1 3.3, J_2 6.3, J_3 8.3, *H*-3), 3.30 (1H, dd, J_1 4.4, J_2 14.7, C*H*Ph), 3.10 (1H, ddd, J_1 4.4, J_2 8.3, J_3 10.0, *H*-4), 2.80 (1H, dd, J_1 10.0, J_2 14.7, C*H*Ph); ^{13}C NMR (100 MHz; $CDCl_3$) δ 176.1 (s, *C*-5), 171.0 (s, *C*OOMe), 137.9 (s, Ph), 128.7 (2 × d, Ph), 128.6 (2 × d, Ph), 126.9 (d, Ph), 67.6 (t, *C*-2), 52.2 (q, O*C*H_3), 44.0 (d, *C*-3), 43.9 (d, *C*-4), 32.4 (t, *C*H_2Ph); *m*/*z* (EI, 70 eV): 234 ($M^{+\cdot}$, 18), 206 (15), 176 (64), 175 (16), 148 (30), 147 (48), 144 (10), 131 (24), 129 (23), 117 (11), 116 (10), 115 (29), 103 (9), 92 (10), 91 (100), 77 (10), 65 (21), 55 (11), 51 (10), 39 (13); *HRMS* (EI, 70 eV): calculated for $C_{13}H_{14}O_4$ ($M^{+\cdot}$) 234.0892, experimental 234.0891. *HRGC* (β-CDX): t_R = 188.6 min for the (3*R*,4*S*) enantiomer and t_R = 203.1 min for the (3*S*,4*R*)-enantiomer (150 °C isotherm); *HRGC* (γ-CDX): t_R = 186.5 min (3*S*,4*R*) enantiomer and t_R = 203.6 min (3*R*,4*S*)-enantiomer (150 °C isotherm).

4.2.8. Methyl *trans*-4-benzyl-5-oxo-3-tetrahydrofurancarboxylate 6b

Esterification of the acid **4b** with diazomethane furnished **6b** as an oil. ν_{max}(film)/cm^{-1} 1776, 1732, 758–698; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.33–7.17 (5H, m, Ph), 4.28 (1H, dd, J_1 8.4, J_2 9.2, *H*-2), 4.21 (1H, dd, J_1 8.8, J_2 9.2, *H*-2), 3.58 (3H, s, O*C*H_3), 3.28–3.14 (3H, m, C*H*Ph + *H*-4 + *H*-3), 3.04 (1H, dd, J_1 6.4, J_2 13.7, C*H*Ph); ^{13}C NMR (100 MHz; $CDCl_3$) δ 176.3 (s, *C*-5), 171.3 (s, *C*OOMe), 136.6 (s, Ph), 129.5 (2 × d, Ph), 128.7 (2 × d, Ph), 127.1 (d, Ph), 67.2 (t, *C*-2), 52.5 (q, O*C*H_3), 44.5 (d, *C*-3), 44.5 (d, *C*-4), 34.7 (t, *C*H_2Ph); *m*/*z* (EI, 70 eV): 234 ($M^{+\cdot}$, 44), 206 (14), 203 (10), 177 (8), 176 (74), 175 (68), 157 (6), 148 (47), 147 (63), 144 (9), 131 (24), 129 (19), 117 (8), 115 (15), 104 (8), 103 (7), 92 (10), 91 (100), 65 (14); *HRMS* (EI, 70 eV) calculated for $C_{13}H_{14}O_4$ ($M^{+\cdot}$) 234.0892, experimental 234.0892; *HRGC* (β-CDX): t_R = 110.4 min for the (3*R*,4*R*) enantiomer and t_R = 113.4 min for the (3*S*,4*S*) enantiomer (150 °C isotherm); *HRGC* (γ-CDX): t_R = 97.4 min for the (3*S*,4*S*) enantiomer and t_R = 102.3 min for the (3*R*,4*R*) enantiomer (150 °C isotherm).

4.3. Enzymatic hydrolyses

To the lactones **5a** and **5b** (1 mmol) in 0.1 M phosphate buffer (14 mL), at pH 7.4, the following amounts of enzymes were added: 0.150 g of Porcine Pancreatic Lipase (PPL, 46,000 U/g), 0.970 g of lipase from *Pseudomonas species* (Amano PS, 30,000 U/g), 0.033 g of lipase from *P. fluorescens* (Amano AK, 30,000 U/g), 0.160 g of lipase from *C. Cylindracea* (CCL, 943,000 U/g), 0.019 g of lipase from *A. niger* (Amano AP 12, 120,000 U/g), 0.330 g of lipase from *C. rugosa* (Amano AY, 30,000 U/g), 0.400 g of lipase from *M. miehei* (MML, Lipozyme), 0.180 g of lipase from *C. antarctica* (Novozyme 435® CAL, 7000 U/g), 0.230 g of Porcine liver acetone powder (PLAP), 0.900 g of Horse liver acetone powder (HLAP), 0.013 g of α-chymotrypsin (α-CT, 79,000 U/g) and 0.086 g of Subtilisin (11,600 U/g). The course of the reaction was monitored with a pH-STAT, with continuous addition of 1.0 M NaOH. At about 20% conversion, the reaction mixture was extracted with ether to separate the unreacted lactone. The mother liquors were acidified with 3.0 N HCl to pH 2 and extracted with ether to obtain the corresponding lactonic acid **1** and/or the lactonic ester **3** derived from the hydroxy halfester intermediate. The organic phases were dried over anhydrous Na_2SO_4 and treated with diazomethane to esterify the carboxylic group before chiral HRGC analysis.

4.3.1. *cis*-(−)-(3*S*,4*R*)-4-Benzyl-5-oxo-3-tetrahydrofurancarboxylic acid 4a

Enzymatic hydrolysis of *cis*-lactonic ester **5a** (0.13 g, 0.5 mmol) was carried out with α-CT (9.0 mg) in 10 mL of phosphate buffer to give, after 6 h (21% conversion), the lactonic acid (−)-**4a** with >99% ee (19 mg, 17% yield), white solid, mp 108–109 °C; $[\alpha]_D^{25} = -103.0$ (*c* 0.93, MeOH); >99% ee (by chiral HRGC analysis on a β-CDX column of its methyl ester **6a**); λ_{max}(MeOH)/nm 211 (5335), 257 (197); CD (MeOH): $\Delta\varepsilon_{217} = -3.7$, $\Delta\varepsilon_{263} = -0.1$. The unreacted ester (+)-**5a** was recovered with 27% ee (97 mg, 75% yield).

4.3.2. Ethyl *cis*-(+)-(3*R*,4*S*)-4-benzyl-5-oxo-3-tetrahydrofurancarboxylate 5a

Enzymatic hydrolysis of *cis*-lactonic ester (+)-**5a** with 27% ee (0.60 g, 0.24 mmol) was carried out with α-CT (5.0 mg) in 10 mL of phosphate buffer to give, after 15.5 h (36% conversion), the unreacted lactonic ester (+)-**5a** with 94% ee (41 mg, 68% yield), oil, $[\alpha]_D^{25} = +124.8$ (*c* 1.4, MeOH); ee 94% (by chiral HRGC on a β-CDX column). λ_{max}(MeOH)/nm 217 (2745), 254 (533); CD (MeOH): $\Delta\varepsilon_{217}$ = +5.0, $\Delta\varepsilon_{262}$ = +0.1. The lactonic acid (−)-**4a** was recovered with 88% ee (20 mg, 38% yield).

4.3.3. *trans*-(−)-(3*S*,4*S*)-4-Benzyl-5-oxo-3-tetrahydrofurancarboxylic acid 4b

Enzymatic hydrolysis of *trans*-lactonic ester **5b** (248 mg, 1 mmol) was carried out with α-CT (15 mg) in 14 mL of phosphate buffer to give, after 56 min (18% conversion), the lactonic acid (−)-**4b** with 92% ee (29 mg, 13% yield), white solid, mp 130–132 °C; $[\alpha]_D^{25} = -29.2$ (*c* 0.24, MeOH); 92% ee (determined by chiral HRGC on a β-CDX column of its methyl ester **6b**); λ_{max}(MeOH)/nm 218 (1311), 258 (172); CD (MeOH): $\Delta\varepsilon_{221}$ = +0.8, $\Delta\varepsilon_{263}$ = +0.03. The unreacted ester (+)-**5b** was recovered with 20% ee (20.4 mg, 82% yield).

4.3.4. Ethyl *trans*-(+)-(3*R*,4*R*)-4-benzyl-5-oxo-3-tetrahydrofurancarboxylate 5b

Enzymatic hydrolysis of *trans*-(+)-lactonic ester **5b** having 17% ee (0.18 g, 0.74 mmol), carried out with α-CT (12.0 mg) in 11 mL

of phosphate buffer, gave after 8.5 h (70% conversion) the unreacted lactonic ester (+)-**5b** with 96% ee (73 mg, yield 40%), oil, $[\alpha]_D^{25} = +34.6$ (*c* 0.24, MeOH); 96% ee (by chiral HRGC on a β-CDX column). λ_{max}(MeOH)/nm 215 (925), 258 (3573); CD (MeOH): $\Delta\varepsilon_{221} = -2.6$, $\Delta\varepsilon_{263} = -0.1$. The lactonic acid (−)-**4b** was recovered with 51% ee (52 mg, 32% yield).

4.4. General procedure for the synthesis of esters 7 and 8

To a solution of 0.13 mmol of the carboxylic acid (−)-**4b** in 1.5 mL of CH_2Cl_2, 40 mg of (*R*) or (*S*)-1-(9-anthryl)-2,2,2-trifluoroethanol was added. EDC (83 mg), Et_3N (0.04 mL) and DMAP (24 mg) were then added. The mixture was kept under stirring for 24 h. At the end of the reaction, CH_2Cl_2 was added, and the organic phase was washed with 5% $KHSO_4$, water, 5% $NaHCO_3$, water, and dried over anhydrous Na_2SO_4. Although the derivatives **7** and **8** obtained were purified by flash chromatography, they were always about 20% of the unreacted 1-(9-anthryl)-2,2,2-trifluoroethanol in an admixture.

4.4.1. (1′*R*,3*S*,4*S*)-1-(9-Anthryl)-2,2,2-trifluoroethyl-4-benzyl-5-oxo-3-tetrahydrofurancarboxylate 7

^{1}H NMR (400 MHz; $CDCl_3$) δ 8.58 (1H, s, Ar), 8.45 (1H, d, *J* 8.8, Ar), 8.25 (1H, d, *J* 9.1, Ar), 8.05 (1H, d, *J* 8.4, Ar), 8.03 (1H, d, *J* 8.4, Ar), 7.68 (1H, q, *J* 7.7, $CHCF_3$), 7.65 (1H, t, *J* 7.7, Ar), 7.50 (3H, m, Ar), 7.22 (3H, m, Ph), 7.15 (2H, m, Ph), 4.19 (1H, t, *J* 9.0, H-2), 4.03 (1H, t, *J* 9.0, H-2), 3.31 (1H, ddd, J_1 9.9, J_2 8.8, 8.4, H-3), 3.21 (1H, ddd, J_1 9.9, J_2 5.4, J_3 8.4, H-4), 3.14 (2H, AB part of an ABX system, CH_2Ph); ^{13}C NMR (100 MHz; $CDCl_3$) δ 175.9 (s, C-5), 169.0 (s, COO), 136.2 (s, Ph), 131.8 (d, Ar), 131.6 (s, Ar), 131.2 (s, Ar), 130.9 (s, Ar), 130.8 (d, Ar), 130.5 (s, Ar), 129.7 (d, Ar), 129.5 (2 × d, Ph), 128.9 (2 × d, Ph), 128.2 (d, Ar), 127.3 (d, Ph), 126.9 (d, Ar), 125.6 (d, Ar), 125.3 (d, Ar), 125.2 (d, Ar), 123.9 (q, J 231, CF_3), 122.2 (d, Ar), 120.1 (s, Ar), 70.0 (q, J 35, *C*HCF_3), 66.6 (t, C-2), 44.4 (d), 44.0 (d), 34.5 (t, CH_2Ph).

4.4.2. (1′*S*,3*S*,4*S*)-1-(9-Anthryl)-2,2,2-trifluoroethyl-4-benzyl-5-oxo-3-tetrahydrofurancarboxylate 8

^{1}H NMR (400 MHz; $CDCl_3$) δ 8.63 (1H, s, Ar), 8.56 (1H, d, *J* 8.8, Ar), 8.26 (1H, d, *J* 9.1, Ar), 8.08 (1H, d, *J* 8.4, Ar), 7.73 (1H, q, *J* 7.9, $CHCF_3$), 7.66 (1H, t, *J* 7.9, Ar), 7.54 (3H, m, Ar), 6.94 (2H, m, Ph), 6.85 (3H, m, Ph), 4.31 (1H, t, *J* 8.4, H-2), 4.19 (1H, t, *J* 8.4, H-2), 3.29 (1H, dt, J_1 9.7, J_2 8.4, H-3), 3.17 (1H, ddd, J_1 9.7, J_2 5.4, J_3 6.5, H-4), 3.03 (1H, dd, J_1 5.4, J_2 14.3, CHPh), 2.92 (1H, dd, J_1 6.5, J_2 14.3, CHPh); ^{13}C NMR (100 MHz; $CDCl_3$) δ 175.9 (s, C-5), 169.1 (s, COO), 135.8 (s, Ph), 131.7 (d, Ar), 131.4 (s, Ar), 131.1 (s, Ar), 130.8 (s, Ar), 130.6 (s, Ar), 129.6 (d, Ar), 129.5 (d, Ar), 129.1 (2 × d, Ph), 128.5 (2 × d, Ph), 128.0 (d, Ar), 126.8 (d, Ph), 126.7 (d, Ar), 125.7 (d, Ar), 125.1 (2d, Ar), 124.0 (q, J 284, CF_3), 122.1 (d, Ar), 120.0 (s, Ar), 69.71 (q, J 35, *C*HCF_3), 66.6 (t, C-2), 44.1 (2d, C-3+C-4), 34.4 (t, CH_2Ph).

4.5. Synthesis of ester 9

4-Bromophenacyl*cis*-(−)-(3*S*,4*R*)-4-benzyl-5-oxo-3-tetrahydrofurancarboxylate 9: To 18 mg (0.08 mmol) of (−)-**4a** with >99% ee, 2 mL of toluene, 12 μL (0.08 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 22.3 mg (0.08 mmol) of 2,4′-dibromoacetophenone were added. After stirring overnight, water and ether were added, and the organic phase was separated and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave 25 mg (0.06 mmol, 75% yield) of (−)-**9**. Crystals of good quality were obtained from a $CDCl_3$/EtOH mixture. White solid, mp 111–112 °C; $[\alpha]_D^{25} = -176.8$ (*c* 0.5, MeOH); ν_{max}(nujol)/cm^{-1} 1771, 1735, 1697; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.75 (2H, d, *J* 8.4), 7.65 (2H, d, *J* 8.4), 7.28 (5H, m, Ph), 5.31 (2H, AB system, J_{AB} 16.3, CO-CH_2O), 4.64 (1H, dd, J_1 2.3, J_2 9.6, *H*-2), 4.35 (1H, dd, J_1 6.3, J_2 9.6, *H*-2), 3.48 (1H, m) 3.34 (1H, dd, J_1 3.7, J_2 13.9,), 3.4–3.0 (2H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ 190.2 (s), 175.9 (s), 170.2 (s), 138.3 (s), 132.5 (s), 132.3 (2 × d), 129.5 (s), 129.2 (2 × d), 128.7 (4 × d), 126.8 (d), 67.7 (t), 66.1 (t), 44.3 (d), 44.0 (d), 32.0 (t); *m*/*z* (EI, 70 eV): 419 (M+H$^+$, 4), 417 (M+H$^+$, 4), 360 (7), 358 (7), 219 (6), 200 (100), 198 (97), 185 (59), 183 (56), 144 (83), 91 (17).

4.6. Conformational analysis

A set of optimized conformations for all the analyzed compounds was obtained by a simple Monte Carlo search. Each rotatable bond was allowed to rotate in order to generate the starting set of geometries. Each bond was twisted by 10° torsional increments randomly, and the initial set was thus obtained. The geometries were optimized first using molecular mechanics calculations with the Cornell version of the Amber forcefield;[20] the optimizations were carried out with the Polak-Ribiere conjugate gradient algorithm to a gradient of 0.001 kcal/Å mol. The first 10 conformations obtained at this first step were then submitted to a further refinement, and their geometries were reoptimized with a semi-empirical calculation using the AM1 Hamiltonian[14] as implemented in Sybyl6.8.[21] The SCF convergence limit for the UHF calculation was set to full accuracy, while the GNORM keyword was set to 0.001. All the calculations were carried out on a Silicon Graphic Octane workstation.

4.7. X-ray crystallography for compound 9

Diffraction data were collected at room temperature on a Nonius DIP-1030H system with Mo Kα radiation ($\lambda = 0.71073$ Å). Cell refinement, indexing and scaling of the data sets were carried out using Denzo and Scalepack.[22] The structure was solved by direct methods and Fourier analyses,[23] and was refined by the full-matrix least-squares method based on F^2.[23] All the calculations were performed using the WinGX System, Ver 1.70.01.[24]

Crystal data: $C_{20}H_{17}BrO_5$, $M = 417.25$, monoclinic, space group $P2_1$, $a = 9.045(3)$, $b = 23.144(4)$, $c = 9.077(3)$ Å, $\beta = 103.64(3)°$, $V = 1846.6(9)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.501$ g/cm^3, μ(Mo–Kα) =2.253 mm^{-1}, $F(000) = 848$. Final $R = 0.0389$, $wR2 = 0.0812$, $S = 0.870$ for 469 parameters and 19,765 reflections, 6306 unique [$R_{(int)} = 0.0460$], of which 3599 with $I > 2\sigma(I)$, max positive and negative peaks in ΔF map 0.277, −0.316 e Å^{-3}. Absolute structure parameter 0.026(8).[25]

Crystallographic data (excluding structure factors) for **9** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 709657. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.]

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