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Chemoenzymatic synthesis of diastereomeric ethyl γ-benzyl paraconates and determination of the absolute configurations of their acids

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Abstract—Enantiopure (99% ee) *cis*- and *trans*-γ-benzylparaconic acids and their ethyl esters were synthesized by a procedure involving kinetic enzymatic resolution of the corresponding lactonic esters with α-chymotrypsin (α-CT) with acetone added as a cosolvent. Their absolute configurations were determined by ^{1}H NMR analysis of their 1-(9-anthryl)-2,2,2-trifluoroethyl esters.

1. Introduction

Interest in the γ-lactone ring relies on the fact that it is part of many enantiopure natural products[1] showing biological activity as antimicrobials, antitumourals, immunomodulators, antifungal, plant growth inhibitors,[2] and as key flavours of aged alcoholic beverages.[3] It can also be found in ubiquitous products present in a variety of fruits and flowers,[4] in insect pheromones,[5] as well as in lignans, a wide class of natural compounds present in plants and in their mammalian metabolites.[6] Paraconic acids constitute a small class of variously functionalized γ-lactones exhibiting antibiotic and antitumoural properties and characterized by the presence of a carboxylic group at the β-position.[7] In the frame of our work aimed at the chemoenzymatic synthesis of some of these systems,[8] we recently investigated the enantiopure synthesis of paraconic acid itself (5-oxo-3-tetrahydrofurancarboxylic acid) and those of its γ-methyl and γ,γ-dimethyl derivatives in enantiomerically pure forms.[9] A few aza-paraconic acid derivatives (5-oxo-3-pyrrolidinecarboxylic acid) have also been studied, among which the *N*-benzyl γ-lactamic ester proved particularly suitable for kinetic resolution with α-chymotrypsin (α-CT), owing to favourable interactions between the enzyme and the benzyl group at nitrogen, as demonstrated by molecular mechanics calculations.[10] Therefore taking advantage of these observations, we took into consideration γ-benzylparaconic acid derivatives, to verify whether the benzyl group on a lactone ring, although located in a different position with respect to the lactam ring, could also interact with the enzyme favourably. Herein, we report the results obtained in the chemoenzymatic syntheses of so far unknown optically active γ-benzylparaconic acids, **1** and **2** (Fig. 1) and in the determination of their absolute configurations.

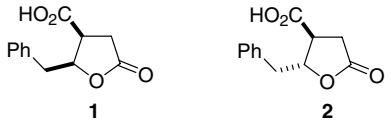

Figure 1. Targeted molecules.

2. Results and discussion

2.1. Synthesis of substrates

Diastereomeric racemic lactonic esters **7** and **8** (Scheme 1) were synthesized from ethyl 3-oxo-4-phenylbutanoate **3**[11] and ethyl bromoacetate under basic conditions. The resulting diethyl phenylacetylsuccinate **4** was reduced with sodium borohydride to give the corresponding

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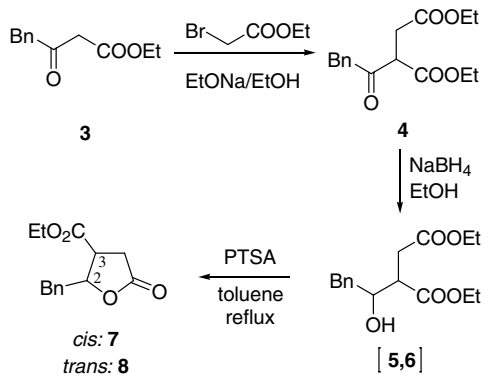


Scheme 1. Synthesis of substrates **7** and **8**.

hydroxydiesters **5** and **6**, which were not isolated, in an admixture with the desired lactones **7** and **8**. Complete lactonization was accomplished by heating the reaction mixture in toluene, in the presence of PTSA as a catalyst. The diastereomeric lactonic esters *cis*-**7** and *trans*-**8**, formed in about a 1:1 ratio, were then separated on column chromatography and subjected to enzymatic hydrolyses separately. Since their ^{13}C NMR spectra were practically superimposable, their geometries were determined by the fact that lactone **7** converted into its stereoisomer **8** almost quantitatively (1:9), as well as by NOE difference measurements. In particular, irradiation of the signal relative to H-3 in compound **7** at 3.46 ppm caused enhancement of the H-2 (6%) signal and that of H-4 at 2.65 ppm (10%). In the *trans* derivative **8**, irradiation of the H-2 signal at 4.87 ppm caused enhancement of the H-4 signal *cis* to the ethoxycarbonyl group at 2.82 ppm (2%), while irradiation of the H-4 signal *trans* to the ethoxycarbonyl group at 2.53 ppm enhanced the H-3 signal at 3.09 ppm (5%). Therefore, since H-2 is *cis* to H-4 at 2.82 ppm and H-3 is *cis* to H-4 at 2.53 ppm, H-2 and H-3 must be *trans* to each other.

2.2. Enzymatic hydrolyses

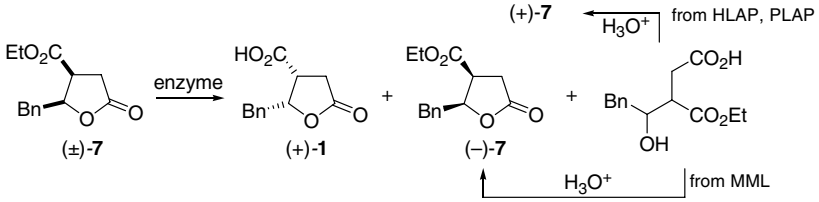
Enzymatic hydrolyses were performed using a series of commercially available enzymes, namely Porcine pancreatic lipase (PPL), lipase from *Pseudomonas* species (PS), lipase from *Pseudomonas fluorescens* (AK), *Candida cylindracea* lipase (CCL), *Aspergillus niger* (AP12), lipase from *Candida rugosa* (AY), *Mucor miehei* lipase (MML), *Candida antarctica* lipase (CAL), porcine liver acetone powder (PLAP), horse liver acetone powder (HLAP), α-chymotrypsin (α-CT) and protease from *Bacillus subtilis* (SUB). The reactions were monitored with a pH-stat instrument by continuous addition of 1 M NaOH. The main results are summarized in Tables 1 and 2.

For *cis* lactone **7** (Table 1), the best results were obtained using α-chymotrypsin, which hydrolyzed the ethoxycarbonyl group exclusively, furnishing the corresponding lactonic acid (+)-**1** with fairly good enantiomeric excess (86%, $E = 16$) (entry 1). The enantioselectivity of the reaction was greatly improved ($E \approx 2400$) by adding acetone as a cosolvent, whose amount was optimized to 5% v/v. Under these conditions (entry 2), acid (+)-**1** was obtained with >99% ee at 17% conversion. Increasing the amount of acetone decreases the enzyme activity as its essential bound water is stripped out from the enzyme's surface.[13]

Other enzymes, such as HLAP, MML and PLAP (Table 1, entries 5–7) furnished less satisfactory results, showing an exclusive preference for ring fission in the former two cases, while with PLAP, the ratio between the hydrolysis product from the ester group and that from the lactone group was 3:7. In all cases however, the enantioselectivity was poor.

Using α-CT and the same conditions as above and leaving the reaction to proceed to high conversion values (60%),

Table 1. Enzymatic hydrolyses[a] of racemic *cis*-lactone **7** at low conversion values



Entry	Enzyme	Acetone (%, v/v)	E	Conv.[b]	Time	Lactonic acid **1**			Unreacted ester **7**			Ester **7** (from ring fission)		
						Sign of α	ee (%)[c]	Abs. config.	Sign of α	ee (%)[d]	Abs. config.	Sign of α	ee (%)[d]	Abs. config.
1	α-CT	0	16	15	7.75 h	(+)	86	2*R*,3*R*	(−)	15	2*S*,3*S*	—	—	—
2		5	2431	17	6.5 h	(+)	>99	2*R*,3*R*	(−)	20	2*S*,3*S*	—	—	—
3		10	9	21	22.5 h	(+)	77	2*R*,3*R*	(−)	21	2*S*,3*S*	—	—	—
4		20	13	9	6.75 h	(+)	85	2*R*,3*R*	(−)	8	2*S*,3*S*	—	—	—
5	HLAP	0	3	25	45 min	—	—	—	(−)	16	2*S*,3*S*	(+)	48	2*R*,3*R*
6	MML	0	3	14	3 min	—	—	—	(−)	7	2*S*,3*S*	(−)	43	2*S*,3*S*
7	PLAP	0	nd	nd	1.5 h	(±)	0	—	(−)	4	2*S*,3*S*	(+)	63	2*R*,3*R*

[a] Conditions: phosphate buffer, pH 7.4, rt.
[b] Calculated.[12]
[c] Determined by chiral HRGC on the methyl ester derivative.
[d] Determined by chiral HRGC.

Table 2. Enzymatic hydrolyses[a] of racemic *trans*-lactone **8** at low conversion values

Entry	Enzyme	Acetone (%, v/v)	*E*	Conv.[b]	Time (h)	Lactonic acid **2**			Unreacted ester **8**		
						Sign of α	ee (%)[c]	Abs. config.	Sign of α	ee (%)[d]	Abs. config.
1	α-CT	0	2.3	35	2.75	(−)	32	2*S*,3*R*	(+)	16	2*R*,3*S*
2		5	12	26	1	(−)	81	2*S*,3*R*	(+)	29	2*R*,3*S*
3		10	15	30	0.5	(−)	83	2*S*,3*R*	(+)	36	2*R*,3*S*
4		20	230	13	2	(−)	99	2*S*,3*R*	(+)	15	2*R*,3*S*
5	PPL	0	3	24	6.4	(−)	56	2*S*,3*R*	(+)	21	2*R*,3*S*
6		20	3	25	7	(−)	62	2*S*,3*R*	(+)	21	2*R*,3*S*
7	CCL	0	3	24	1	(+)	44	2*R*,3*S*	(−)	14	2*S*,3*R*
8		20	5	11	5	(+)	66	2*R*,3*S*	(−)	8	2*S*,3*R*
9	AY	0	4	31	2	(+)	49	2*R*,3*S*	(−)	22	2*S*,3*R*
10		20	3	19	4	(+)	43	2*R*,3*S*	(−)	10	2*S*,3*R*
11	CAL	0	5	46	8	(−)	50	2*S*,3*R*	(+)	43	2*R*,3*S*
12		20	7	35	7.25	(−)	66	2*S*,3*R*	(+)	36	2*R*,3*S*

[a] Conditions: phosphate buffer, pH 7.4, rt.
[b] Calculated.[12]
[c] Determined by chiral HRGC on the methyl ester derivative.
[d] Determined by chiral HRGC.

the unreacted lactonic ester (2*S*,3*S*)-(−)-**7** was obtained with >99% ee.

Conversely, hydrolyses of the *trans* lactonic ester **8** were completely regioselective with all the enzymes used, leading to lactonic acid **2** as the only product (Table 2). Again the best results were obtained with α-CT and again using acetone as a cosolvent, but in this case in an amount of 20% v/v. In this manner, lactonic acid (−)-**2** with >99% ee was isolated (entry 4). The presence of the cosolvent was also useful for the other enzymes listed in Table 2, as a slight but visible improvement in the enantiomeric excess of the product was observed.

The enzymes PPL and CAL showed the same enantiopreference as α-CT, leading to the laevorotatory enantiomer of lactonic acid (−)-**2**, while CCL and AY showed an opposite enantiopreference leading to acid (+)-**2**.

Enzymes HLAP, PLAP, SUB, Lipase PS, Lipase AK and MML were also checked but all gave the product with very low ee's or as racemates.

Using α-CT and leaving the reaction to proceed to high conversion values (61%), the unreacted ester (2*R*,3*S*)-(+)-**8** was obtained with >99% ee.

2.3. Determination of the absolute configurations of the products

Of the several methods proposed in the literature to assign the absolute configuration to optically active carboxylic acids,[14] we considered the method recently proposed by Riguera et al., which looked attractive for its easiness and generality.[15] In this work, the absolute configuration of the α-carbon of a carboxylic acid is assigned from the values of the shielding effects observed in the ^{1}H NMR spectra of its esters with (*R*)-(−)- and (*S*)-(+)-(1-(9-anthryl)-2,2,2-trifluoro)ethanol.

The core assumption of the method is that the ground state conformation of such esters is that shown in Figure 2, namely with the ester carbonyl group eclipsed with the hydrogen atom of the known alcohol stereocentre and antiperiplanar (ap) with the hydrogen atom of the stereocentre whose configuration has to be determined (conformers **a** and **c**, Fig. 2). Owing to the fact that the aromatic ring is coplanar with the proton at C1′, this particular arrangement would cause a shielding of the protons belonging to the group lying on the same side as the aromatic group, namely (L^1 for conformer **a** and L^2 for conformer **c**). A conformer can be envisaged in each case in which the carbonyl group is synperiplanar (sp) with the hydrogen atom of the stereocentre to be determined (conformers **b** and **d**, Fig. 2), but conformers **a** and **c** prevail over the corresponding **b** and **d**, as demonstrated by Riguera with several conformational analyses carried out with molecular mechanics and with the semiempirical Hamiltonians AM1 and PM3.[15] The absolute configuration of the stereocentre bearing L^1 and L^2 can thus be determined from the differences in chemical shift of the corresponding protons observed for the two diastereomers ($\Delta\delta^{R,S}$).

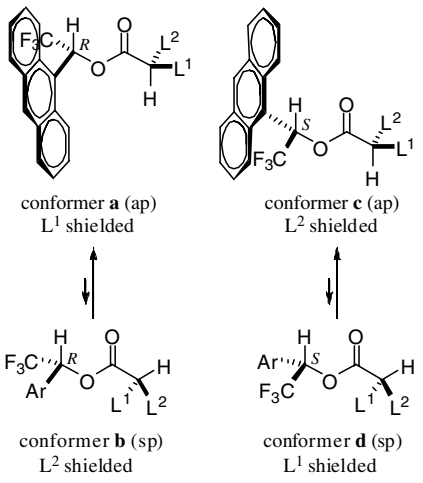
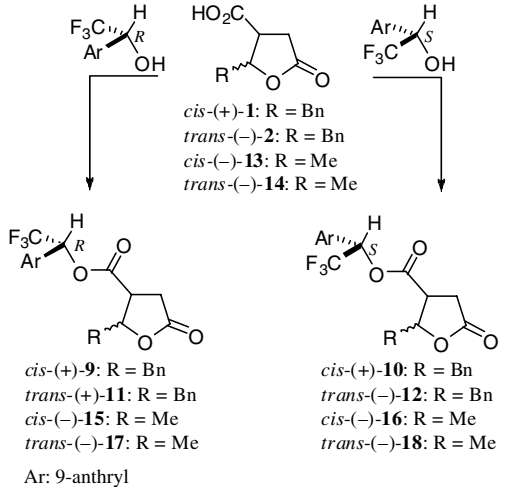


Figure 2. Riguera's models.

For the protons on L^1, a negative value of $\Delta\delta^{R,S}$ is obtained, while the protons on L^2 show a positive $\Delta\delta^{R,S}$.

This method was validated by Riguera on a set of more than 20 linear acids. However, the energy difference between the conformers found by Riguera's calculations was always small, in the order of 1 kcal/mol.

Moreover, a preliminary conformation analysis carried out on the Riguera esters of our lactonic acids lead to the identification of at least four different conformers for each lactone, and in several conformations, the orientation of the anthryl group does not seem to be relevant as to a shielding effect on the L^1 and L^2 groups. For these reasons we have decided to synthesize the Riguera esters of lactones **1** and **2**, as well as of reference lactones **13** and **14** (Scheme 2), whose absolute configurations are known to be (2*S*,3*S*) and (2*S*,3*R*), respectively,[9] and to submit all the molecules to a more careful conformational analysis.



Scheme 2. Riguera's esters from lactones (+)-**1**, (−)-**2**, (−)-**13** and (−)-**14**.

The optically active lactonic acids (+)-**1**, (−)-**2**, (−)-**13** and (−)-**14** were thus reacted with commercially available (*R*)-(−)- and (*S*)-(+)-(1-(9-anthryl)-2,2,2-trifluoro)ethanol. The eight stereoisomers thus obtained, namely (+)-**9**, (+)-**10**, (+)-**11**, (−)-**12**, (−)-**15**, (−)-**16**, (−)-**17** and (−)-**18** (Scheme 2), were analyzed by ^{1}H NMR spectroscopy. ^{1}H NMR spectra of all compounds were analyzed thoroughly by means of 2D experiments and spin–spin decoupling experiments in order to have a complete proton assignment.

Table 3 lists the chemical shift of the protons involved in the shielding effect by the diamagnetic anisotropy of the anthrylic group, while Figure 3 shows the assigned configurations for the *cis* diastereomers, for a better comprehension. From the chemical shifts of H-3 in their respective diastereomeric pairs **9/10**, **11/12**, **15/16** and **17/18**, it is evident that its orientation remains fixed and it does not depend on the configuration of the chiral auxiliary, thus supporting the conformations proposed. The same can be said for the anthryl substituent, whose carbon resonances remain practically identical for all compounds. Comparison of the ^{1}H NMR spectra of esters **15** and **16** (entries 5 and 6), derived from the reference lactone (2*S*,3*S*)-**13**, yields a negative value of $\Delta\delta^{R,S}$ for both the methine proton at C2 and the methyl group on the same carbon, while a positive $\Delta\delta^{R,S}$ is observed for the methylene protons at C4. On the contrary, esters **17** and **18**, derived from lactone (2*S*,3*R*)-**14**, show a positive $\Delta\delta^{R,S}$ for both the C2 proton and methyl, and a negative $\Delta\delta^{R,S}$ for the C4 methylene (entries 7 and 8). The opposite shielding effects thus indicate a different configuration at C3 for the two pairs of reference esters, while the application of Riguera rules lead to the correct assignment of (*S*)-absolute configuration at C3 for **15** and **16**, and (*R*)- for **17** and **18**. The four diastereomeric esters have been submitted to an extensive conformational

Table 3. Chemical shifts and $\Delta\delta^{R,S}$ for the protons affected by the diamagnetic anisotropy of the aromatic ring

Entry	Compd	H-3	H-2		H-4				CH_2Ph		CH_3	
		δ (ppm)	δ (ppm)	$\Delta\delta^{R,S}$	H-4 *cis* to COOR	$\Delta\delta^{R,S}$	H-4 *trans* to COOR	$\Delta\delta^{R,S}$	δ, ppm	$\Delta\delta^{R,S}$	δ, ppm	$\Delta\delta^{R,S}$
1	(1′*R*,2*R*,3*R*)-**9**	3.64	4.92	+0.14	2.76	−0.12	2.68	−0.06	2.77[a]	+0.38		
2	(1′*S*,2*R*,3*R*)-**10**	3.73	4.78		2.88		2.74		2.39[a]			
3	(1′*R*,2*S*,3*R*)-**11**	3.26	4.88	+0.15	2.70	−0.14	2.52	−0.08	3.14[a]	+0.16		
4	(1′*S*,2*S*,3*R*)-**12**	3.28	4.73		2.84		2.60		2.98[a]			
5	(1′*R*,2*S*,3*S*)-**15**	3.63	4.76	−0.20	2.90	+0.03	2.70	+0.09			0.83	−0.53
6	(1′*S*,2*S*,3*S*)-**16**	3.59	4.96		2.87		2.61				1.36	
7	(1′*R*,2*S*,3*R*)-**17**	3.19	4.69	+0.16	2.79	−0.17	2.77	−0.12			1.60	+0.19
8	(1′*S*,2*S*,3*R*)-**18**	3.20	4.53		2.96		2.89				1.41	

[a] Average chemical shift of the two geminal protons.

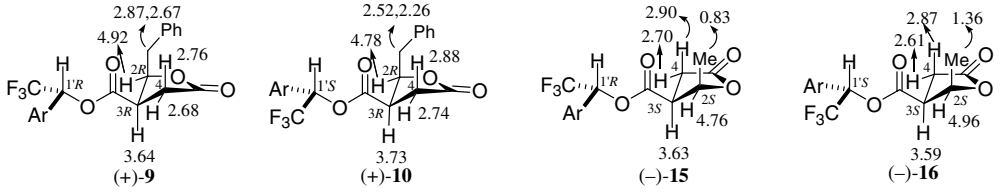


Figure 3. Stereochemistry and ^{1}H NMR data of interest for Riguera's derivatives (+)-**9**, (+)-**10**, (−)-**15** and (−)-**16**.

search, carried out with a Monte Carlo algorithm operating on PM3 geometry optimizations.[16]

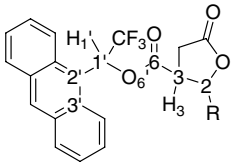
We have found two energy minima for each compound, and the absolute minimum was always that identified by Riguera (Table 4), the other being very close in energy. Nevertheless, after obtaining and considering the population of each conformation by Boltzmann statistics at room temperature (Table 4), a qualitative analysis of the shielding effects on each conformer leads to the correct predictions.

The anthryl group is approximately coplanar with H1′ (Table 4, C3′C2′C1′H1′ dihedral angle). This orientation assures that the cone of diamagnetic anisotropy (hemiangle 45°) affects only the protons lying on the same side as the aromatic moiety and located 4 or 5 bonds away from the C1′ stereocentre.[15a,c]

The esters of the *cis*- and *trans*-lactones **9**–**12** of unknown configuration at C3, show the same shielding effect (Table 3), thus suggesting that both the *cis* and *trans* derivatives have the same configuration at C3. According to the Riguera rules, the absolute configuration at this centre should be *R*. The conformational analysis confirms this prediction, although the picture here is much more complicated than in the simple Riguera explanation. The analysis was carried out on the model structures of the (3*R*) lactone esters. Also due to the presence of the benzyl group at the 2-position of the lactone rings, multiple minima have been obtained.

The (1′*R*)-ester **9** of *cis* lactone **1** shows four conformations close in energy, while the ground conformation 0 (Table 4) only represents 47% of the lactone population at room temperature. A shielding effect on the protons at C2 can be predicted for this conformation, as well as for conformation 2. Thus, C2 is shielded in about 73% of the population of this compound, while the shielding effects operate on C4 in the remaining 27%. The (1′*S*) ester **10** of the same lactone shows a very different conformational space, and although four minima are also found for this compound,

Table 4. PM3 conformation analysis of esters **9**–**12** and **15**–**18**: structures, energies and predicted shielding effects



Compd	Conf.	$C_{3'}C_{2'}C_{1'}H_{1'}$ (°)	$H_{1'}C_{1'}O_{6'}C_6$ (°)	$O_6C_6C_3H_3$ (°)	PM3 $\Delta H_{f,rel\,(absolute)}$ (kcal/mol)	Population (%)	Shielding on C2	Shielding on C4	Predicted $\Delta\delta^{R,S}$ on C2	Predicted $\Delta\delta^{R,S}$ on C4
(1′*R*,2*R*,3*R*)-**9**	0	183.9	23.3	358.1	0 (−221.86)	47.1	Y	N		
	1	182.5	11.8	158.9	0.33	27.0	N	Y		
	2	186.7	30.6	351.5	0.38	25.0	Y	N		
	3	187.7	32.9	135.4	2.3	0.9	N	Y		
(1′*S*,2*R*,3*R*)-**10**	0	158.1	337.6	156.1	0 (−224.04)	99.87	Y	N	>0	<0
	1	171.2	1.8	5.0	4.0	0.12	N	Y		
	2	176.2	2.4	0.1	6.0	1×10^{-3}	N	Y		
	3	156.4	343.5	146.7	7.1	6×10^{-4}	Y	N		
(1′*R*,2*S*,3*R*)-**11**	0	202.0	357.4	159.4	0 (−227.90)	85.8	N	N		
	1	201.4	358.6	162.3	1.2	10.7	N	N		
	2	200.7	14.6	174.1	2.5	1.4	N	Y		
	3	199.6	16.1	4.4	2.5	1.3	Y	N		
	4	199.7	16.5	1.3	3	0.5	Y	N		
	5	187.4	28.5	3.6	3.4	0.3	Y	N		
(1′*S*,2*S*,3*R*)-**12**	0	162.8	326.9	170.0	0 (−226.74)	63.0	Y	N	>0	<0
	1	164.9	335.6	2.0	0.8	16.0	N	Y		
	2	172.5	330.6	149.0	1.2	8.4	Y	N		
	3	171.3	3.0	193.8	1.3	7.3	Y	N		
	4	165.7	323.9	355.7	1.8	3.1	N	Y		
	5	165.6	329.7	356.3	2.0	2.1	N	Y		
(1′*R*,2*S*,3*S*)-**15**	0	181.2	10.4	178.4	0 (−251.47)	98.2	Y	N		
	1	183.9	8.7	5.3	2.4	1.8	N	Y		
(1′*S*,2*S*,3*S*)-**16**	0	185.2	13.2	175.8	0 (−251.80)	89.8	N	Y	<0	>0
	1	184.3	4.7	2.1	1.2	10.2	Y	N		
(1′*R*,2*S*,3*R*)-**17**	0	172.4	22.5	183.1	0 (−254.33)	72.0	N	Y		
	1	186.8	22.1	5.7	0.5	28.0	Y	N		
(1′*S*,2*S*,3*R*)-**18**	0	184.2	3.8	185.7	0 (−253.82)	90.0	Y	N	>0	<0
	1	187.6	9.2	3.3	1.3	10.0	N	Y		

its ground conformation 0 is almost the only one populated at room temperature (Table 4). This conformation corresponds to that predicted by Riguera, and the shielding effect of the anthryl group operates on C2. If we compare the populations of conformers shielding on C2 and C4 in the (1′*R*) and (1′*S*) esters, we can then predict a positive $\Delta\delta^{R,S}$ on C2 and a negative $\Delta\delta^{R,S}$ on C4. These predictions are in agreement with the experimental values of $\Delta\delta^{R,S}$ reported in Table 3, and for this reason the absolute configuration (*R*)- is assigned to carbon 3. Due to the *cis* relationship between the substituents at C3 and C2, it follows that C2 also has an (*R*)-configuration.

The (1′*R*)-ester **11** of the *trans* lactone **2** shows six energy minima, and in the first two conformations 0 and 1 (more than 96% of the total population at room temperature), the anthryl group is arranged in such a way that there is no shielding effect on any proton of the molecule (Table 4). The (1′*S*) ester **12** of the same lactone shows also six minima, but this time the ground conformation (63% of the population) obeys Riguera's prediction and is shielded at C2. The same shielding effect was also observed for the third conformation of this compound (8%). Thus, by comparing the irrelevant shielding effects on the (1′*R*) ester with the effects on the (1′*S*) derivative, we can predict a positive $\Delta\delta^{R,S}$ at C2, and a negative $\Delta\delta^{R,S}$ at C4 also for the *trans* pair. Again the predictions are in agreement with the experimental data reported in Table 3, and thus we assigned the (*R*)-configuration to C3 also for the *trans* lactones, whose configuration at C2 must be (*S*).

3. Experimental

3.1. 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 Hz. Optical rotations were determined on a Perkin Elmer Model 241 polarimeter. CD spectra were obtained on a Jasco J-700 A spectropolarimeter (0.1 cm cell). GC analyses were run on a Carlo Erba GC 8000 instrument and on a Shimadzu GC-14B instrument, 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). Enzymic hydrolyses were performed using a pH-stat Controller PHM290 Radiometer Copenhagen. Mass spectra were recorded on a VG 7070 (70 eV) spectrometer. HRMS spectra were performed on a Finnigan MAT95XP spectrometer. TLC's 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. Benzoyl chloride and Meldrum's acid were purchased from Sigma–Aldrich.

Compound **3** was prepared by acylation of Meldrum's acid, followed by hydrolysis, in accordance with the literature.[17]

The ketodiester **4** was prepared from compound **3**, in accordance with the literature procedure used for the dimethyl analogue.[18]

3.1.1. Diethyl phenylacetylsuccinate 4. Colourless oil, bp 175–177 °C (1 mmHg); IR (neat): 1732, 1502, 1412, 1259, 1184, 698; ^{1}H NMR, δ: 7.35–7.20 (5H, m, Ph), 4.25–4.05 (5H, 2q + m, 2OC*H*$_2$CH$_3$, CH), 4.01, 3.95 (2H, AB system, CH$_2$Ph), 2.90 (2H, part AB of an ABX system, $J_{AB} = 17.5$ Hz, CH$_2$COO), 1.26, 1.23 (6H, 2t, 2OCH$_2$C*H*$_3$); ^{13}C NMR, δ: 201.3 (s, C=O), 170.9 (s, COO), 168.9 (s, COO), 133.1 (s, Ph), 129.5 (2d, Ph), 128.3 (2d, Ph), 126.9 (d, Ph), 61.5 (t, OCH$_2$), 60.6 (t, OCH$_2$), 53.0 (d, CH), 49.2 (t, CH$_2$COO), 32.3 (t, CH$_2$Ph), 13.8 (q, CH$_3$), 13.7 (q, CH$_3$); MS, *m*/*z*: 293 (100, M$^+$·), 275 (2), 259 (3), 246 (43), 231 (7), 219 (27), 218 (24), 201 (23), 173 (77), 155 (5), 145 (45), 127 (27), 118 (28), 99 (17), 91 (42), 65 (13), 55 (5); HRMS (EI) calcd for C$_{16}$H$_{20}$O$_5$ (M$^+$), 292.1311, found 292.1302.

3.2. Reduction of the ketodiester 4 with NaBH$_4$

A mixture of 1.07 g (3.65 mmol) of **4** and 92 mg of NaBH$_4$ in 3.5 mL of ethanol was kept under stirring for 4 h at room temperature. After the usual workup, a mixture of the corresponding hydroxyesters **5** and **6** and lactones **7** and **8** was obtained. Conversion of the hydroxyesters into the corresponding lactones was accomplished by refluxing in toluene and *p*-toluenesulfonic acid for 2 h. Compounds **7** and **8** were obtained in the ratio of 53:47, respectively, determined by ^{1}H NMR analysis. Equilibration of the mixture with DBU changed the ratio to 1:9, respectively. The diastereoisomers were then separated by flash-chromatography (eluent: light petroleum–ethyl acetate 9:1).

3.2.1. Ethyl *cis*-2-benzyltetrahydro-5-oxo-3-furancarboxylate 7. Colourless solid, mp 70–74 °C; IR (nujol): 1776, 1732; ^{1}H NMR, δ: 7.29–7.19 (5H, m, Ph), 4.87 (1H, part X of an ABX system, $J_{2,3} = 7.3$ Hz, $J_{AX} = 5.0$ Hz, $J_{BX} = 7.9$ Hz, H-2), 4.16, 4.15 (2H, 2q, $J = 6.9$ Hz, OC*H*$_2$CH$_3$), 3.47 (1H, part X of an ABX system, $J_{2,3} = 7.3$ Hz, $J_{AX} = 5.4$ Hz, $J_{BX} = 8.6$ Hz, H-3), 2.94 (1H, part A of an ABX system, $J_{AB} = 14.6$ Hz, $J_{AX} = 5.0$ Hz, CHPh), 2.92 (1H, part B of an ABX system, $J_{AB} = 14.6$ Hz, $J_{BX} = 7.9$ Hz, CHPh), 2.85 (1H, part A of an ABX system, $J_{AB} = 17.6$ Hz, $J_{AX} = 5.4$ Hz, H-4 *cis* to the ethoxycarbonyl group), 2.66 (1H, part B of an ABX system, $J_{AB} = 17.6$ Hz, $J_{BX} = 8.6$ Hz, H-4 *trans* to the ethoxycarbonyl group), 1.25 (3H, t, $J = 7.1$ Hz, OCH$_2$C*H*$_3$); ^{13}C NMR, δ: 174.2 (s, C-5), 170.8 (s, COOEt), 134.9 (s, Ph), 129.8 (d, Ph), 128.6 (2d, Ph), 127.2 (d, Ph), 81.5 (d, C-2), 61.7 (t, O*C*H$_2$CH$_3$), 44.4 (d, C-3), 40.3 (t, CH$_2$Ph), 32.0 (t, C-4), 14.0 (q, OCH$_2$*C*H$_3$); MS, *m*/*z*: 249 (13, MH$^+$), 230 (15), 203 (18), 202 (91), 185 (32), 184 (66), 174 (37), 173 (17), 158 (18), 157 (20), 156 (29), 130 (16), 129 (100),

128 (16), 101 (42), 91 (44), 83 (33), 65 (15), 55 (18); HRMS (EI) calcd for $C_{14}H_{16}O_4$ (M^+), 248.1049, found 248.1048.

3.2.2. Ethyl *trans*-2-benzyltetrahydro-5-oxo-3-furancarboxylate 8. Yellow oil, IR (film): 1776, 1732; ^{1}H NMR, δ: 7.35–7.20 (5H, m, Ph), 4.87 (1H, part X of an ABX system, $J_{2,3} = 7.3$ Hz, $J_{AX} = 5.1$ Hz, $J_{BX} = 5.9$ Hz, H-2), 4.13, 4.12 (2H, 2q, $J = 6.9$ Hz, OCH_2CH_3), 3.15 (1H, part A of an ABX system, $J_{AB} = 14.3$ Hz, $J_{AX} = 5.1$ Hz, CHPh), 3.09 (1H, part X of an ABX system, $J_{2,3} = 7.3$ Hz, $J_{AX} = 8.8$ Hz, $J_{BX} = 9.5$ Hz, H-3), 3.06 (1H, part B of an ABX system, $J_{AB} = 14.3$ Hz, $J_{BX} = 5.9$ Hz, CHPh), 2.82 (1H, part A of an ABX system, $J_{AB} = 17.9$ Hz, $J_{AX} = 8.8$ Hz, H-4 *cis* to the ethoxycarbonyl group), 2.53 (1H, part B of an ABX system, $J_{AB} = 17.6$ Hz, $J_{BX} = 9.5$ Hz, H-4 *trans* to the ethoxycarbonyl group), 1.24 (3H, t, $J = 7.1$ Hz, OCH_2CH_3); ^{13}C NMR, δ: 174.3 (s, C-5), 170.9 (s, COOEt), 134.9 (s, Ar), 129.8 (d, Ar), 128.7 (2d, Ar), 127.2 (d, Ar), 81.6 (d, C-2), 61.8 (t, CH_3CH_2O), 44.5 (d, C-3), 40.4 (t, CH_2Ph), 32.1 (t, C-4), 14.1 (CH_3CH_2O); MS, *m*/*z*: 249 (60, MH^+), 231 (14), 210 (15), 209 (100), 202 (20), 191 (29), 185 (18), 184 (30), 174 (13), 157 (13), 129 (63), 117 (12), 101 (29), 91 (43), 83 (22), 65 (12), 55 (17); HRMS (EI) calcd for $C_{14}H_{16}O_4$ (M^+), 248.1049, found 248.1048.

3.3. Enzymatic hydrolyses

Enzymatic hydrolysis of *cis*-lactonic ester **7** (880 mg, 3.54 mmol) carried out with α-CT (42.5 mg) as the hydrolytic enzyme in 4.0 mL of acetone and 76.0 mL of phosphate buffer gave after 26 h (17% conversion) the lactonic acid, (+)-**1** with >99% ee.

3.3.1. (2*R*,3*R*)-(+)-2-Benzyltetrahydro-5-oxo-3-furancarboxylic acid 1. White solid, mp 147–149 °C; IR (nujol): 1776, 1716; ^{1}H NMR, δ: 7.35–7.20 (5H, m, Ar), 4.89 (1H, part X of an ABX system, $^3J_{2,3} = 7.2$ Hz, $J_{AX} = 3.8$ Hz, $J_{BX} = 9.3$ Hz, H-2), 3.53 (1H, apparent dt, $^3J_{2,3} = 7.2$ Hz, $J_{AX} = 5.2$ Hz, $J_{BX} = 8.4$ Hz, H-3), 3.05 (1H, part A of an ABX system, $J_{AB} = 14.6$ Hz, $J_{AX} = 8.6$ Hz, CHPh), 3.01 (1H, part B of an ABX system, $J_{AB} = 14.6$ Hz, $J_{BX} = 9.3$ Hz, CHPh), 2.87 (1H, part A of an ABX system, $J_{AB} = 17.9$ Hz, $J_{AX} = 5.2$ Hz, H-4 *cis* to the carboxy group), 2.72 (1H, part B of an ABX system, $J_{AB} = 17.9$ Hz, $J_{BX} = 8.4$ Hz, H-4 *trans* to the carboxy group); ^{13}C NMR, δ: 175.1 (s, COOH), 174.3 (s, C-5), 135.8 (s, Ph), 129.2 (2d, Ph), 128.7 (2d, Ph), 127.2 (d, Ph), 80.5 (d, C-2), 44.0 (d, C-3), 37.5 (t, CH_2Ph), 32.0 (t, C-4); MS, *m*/*z*: 220 (4, $M^{+\cdot}$), 202 (69), 184 (77), 174 (41), 158 (22), 156 (36), 130 (23), 129 (44), 117 (16), 115 (15), 101 (29), 92 (51), 91 (100), 83 (41), 65 (19), 55 (25); $[\alpha]_D^{25} = +125.6$ (*c* 0.16, CH_3OH); HRMS (EI) calcd for $C_{12}H_{12}O_4$ (M^+), 220.0736, found 220.0731.

Enzymatic hydrolysis of *cis*-lactonic ester **7** (720 mg, 2.90 mmol), carried out in 66.5 mL of phosphate buffer with 3.5 mL of acetone added, using α-CT (34.8 mg) as the hydrolytic enzyme gave, after 4 days (60% conversion) the unreacted lactone (−)-**7** with 99% ee; $[\alpha]_D^{25} = -79.4$ (*c* 0.34, CH_3OH).

Enzymatic hydrolysis of the *trans*-lactonic ester **8** (300 mg, 1.2 mmol) with α-CT (14.4 mg) as the hydrolytic enzyme in 6.0 mL of acetone and 24.0 mL of phosphate buffer gave after 30 min (13% conversion), (−)-**2** with >99% ee.

3.3.2. (2*S*,3*R*)-(−)-2-Benzyltetrahydro-5-oxo-3-furancarboxylic acid 2. White solid, mp 159–160 °C; IR (nujol): 1776, 1716; ^{1}H NMR, δ: 7.35–7.23 (5H, m, Ar), 4.91 (1H, part X of an ABX system, $J_{2,3} = 6.9$ Hz, $J_{AX} = 4.6$ Hz, $J_{BX} = 6.1$ Hz, H-2), 3.14 (1H, apparent dt, $J_{2,3} = 6.9$ Hz, $J_{AX} = 8.1$ Hz, $J_{BX} = 9.5$ Hz, H-3), 3.18 (1H, part A of an ABX system, $J_{AB} = 14.5$ Hz, $J_{AX} = 4.6$ Hz, CHPh), 3.03 (1H, part B of an ABX system, $J_{AB} = 14.5$ Hz, $J_{BX} = 6.1$ Hz, CHPh), 2.83 (1H, part A of an ABX system, $J_{AB} = 17.9$ Hz, $J_{AX} = 8.1$ Hz, H-4 *cis* to the carboxy group), 2.53 (1H, part B of an ABX system, $J_{AB} = 17.9$ Hz, $J_{BX} = 9.5$ Hz, H-4 *trans* to the carboxy group); ^{13}C NMR, δ: 175.6 (s, COOH), 174.0 (s, C-5), 134.6 (s, Ph), 129.9 (d, Ph), 128.8 (2d, Ph), 127.4 (d, Ph), 81.2 (d, C-2), 43.8 (d, C-3), 40.2 (t, CH_2Ph), 31.7 (t, C-4); MS, *m*/*z*: 220 (4, $M^{+\cdot}$), 202 (66), 184 (54), 176 (15), 174 (30), 158 (12), 156 (13), 129 (17), 101 (38), 92 (62), 91 (100), 83 (51), 65 (18), 55 (20); $[\alpha]_D^{25} = -49.0$ (*c* 0.20, CH_3OH); HRMS (EI) calcd for $C_{12}H_{12}O_4$ (M^+), 220.0736, found 220.0735.

Enzymatic hydrolysis of the *trans*-lactonic ester **8** (1.24 g, 5.0 mmol) was carried out with α-CT (60 mg) as the hydrolytic enzyme in 16 mL of acetone and 64 mL of phosphate buffer, gave after 1 h (61% conversion), (+)-**8** with >99% ee; $[\alpha]_D^{25} = +19.6$ (*c* 0.24, CH_3OH).

3.4. General procedure for the synthesis of the carboxylic acid derivatives (+)-9, (+)-10, (+)-11, (−)-12 and (−)-15, (−)-16, (−)-17, (−)-18

To a solution of 0.13 mmol of the carboxylic acid (+)-**1**, (−)-**2**, (−)-**13** or (−)-**14** in 1.5 mL of CH_2Cl_2, 40 mg (0.14 mmol) of (*R*)-(−)- or (*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol was added. EDC·HCl (83 mg, 0.43 mmol), Et_3N (0.04 mL, 0.28 mmol) and DMAP (24 mg, 0.20 mmol) 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 a 5% solution of $KHSO_4$, water, 5% solution of $NaHCO_3$, water and dried over anhydrous Na_2SO_4. The ester was purified by flash chromatography (eluent: light petroleum–ethyl acetate 9:1).

3.4.1. (1′*R*,2*R*,3*R*)-(+)-1-(9-Anthryl)-2,2,2-trifluoroethyl 2-benzyltetrahydro-5-oxo-3-furancarboxylate 9. IR ($CHCl_3$): 1786, 1766 cm^{-1}; ^{1}H NMR, δ: 8.62 (1H, s, Ar), 8.58 (1H, d, $J = 9.5$ Hz, Ar), 8.36 (1H, d, $J = 8.8$ Hz, Ar), 8.08 (1H, d, $J = 4.0$ Hz, Ar), 8.06 (1H, d, $J = 3.7$ Hz, Ar), 7.90 (1H, q, $J = 8.1$ Hz, $CHCF_3$), 7.69 (1H, m, Ar), 7.62 (1H, m, Ar), 7.54 (2H, m, Ar), 7.18 (3H, m, Ph), 6.99 (2H, m, Ph), 4.92 (1H, ddd, $J_{2,3} = 7.3$ Hz, $J_{AX} = 3.5$ Hz, $J_{BX} = 9.6$ Hz, H-2, part X of an ABX system), 3.64 (1H, ddd, $J_{2,3} = 7.3$ Hz, $J_{AX} = 5.3$ Hz, $J_{BX} = 8.9$ Hz, H-3, part X of an ABX system), 2.87 (1H, part A of an ABX system, $J_{AX} = 3.5$ Hz, $J_{AB} = 14.6$ Hz, CHPh), 2.76 (1H, part A of an ABX system, $J_{AB} = 17.9$ Hz, $J_{AX} = 5.3$ Hz, H-4 *cis* to

the alkoxycarbonyl group), 2.68 (1H, part B of an ABX system, $J_{AB} = 17.9$ Hz, $J_{BX} = 8.9$ Hz, H-4 *trans* to the alkoxycarbonyl group), 2.67 (1H, dd, part B of an ABX system, $J_{AB} = 14.6$ Hz, $J_{BX} = 9.6$ Hz, CHPh); ^{13}C NMR, δ: 173.8 (s, C-5), 168.6 (s, COO), 135.7 (s, Ph), 132.0 (d, Ar), 131.8 (s, Ar), 131.6 (s, Ar), 131.1 (s, Ar), 130.7 (s, Ar), 129.8 (d, Ar), 129.5 (d, Ar), 129.2 (2d, Ph), 128.6 (2d, Ph), 128.2 (d, Ar), 127.1 (d, Ar), 127.0 (d, Ph), 125.9 (d, Ar), 125.3 (2d, Ar), 124.1 (q, $^1J_{CF} = 282$ Hz, CF_3), 122.2 (d, Ar), 120.0 (s, Ar), 80.5 (d, C-2), 69.8 (q, $^2J_{CF} = 31$ Hz, $CHCF_3$), 44.3 (d, C-3), 37.4 (t, CH_2Ph), 31.9 (t, C-4); MS, *m/z*: 479 (20, M+1), 478 (65, $M^{+\cdot}$), 291 (10), 260 (30), 259 (100), 239 (23), 207 (36), 191 (24); $[\alpha]_D^{25} = +86.7$ (*c* 0.15, $CHCl_3$).

3.4.2. (1′*S*,2*R*,3*R*)-(+)-1-(9-Anthryl)-2,2,2-trifluoroethyl 2-benzyltetrahydro-5-oxo-3-furancarboxylate 10. IR ($CHCl_3$): 1786, 1766 cm^{-1}; ^{1}H NMR, δ: 8.64 (1H, d, $J = 8.0$ Hz, Ar), 8.60 (1H, s, Ar), 8.37 (1H, d, $J = 8.8$ Hz, Ar), 8.06 (2H, d, $J = 8.0$ Hz, Ar), 7.96 (1H, q, $J = 7.9$ Hz, $CHCF_3$), 7.66 (2H, m, Ar), 7.55 (1H, d, $J = 6.6$ Hz, Ar), 7.53 (1H, d, $J = 8.4$ Hz, Ar), 7.05 (3H, m, Ph), 6.64 (2H, m, Ph), 4.78 (1H, ddd, $J_{2,3} = 7.3$ Hz, $J_{AX} = 9.7$ Hz, $J_{BX} = 3.7$ Hz, H-2, part X of an ABX system), 3.73 (1H, dt, $J_{2,3} = 7.3$ Hz, $J_{AX} = 6.8$ Hz, $J_{BX} = 8.9$ Hz, H-3, part X of an ABX system), 2.88 (1H, part A of an ABX system, $J_{AB} = 17.6$ Hz, $J_{AX} = 6.8$ Hz, H-4 *cis* to the alkoxycarbonyl group), 2.74 (1H, part B of an ABX system, $J_{AB} = 17.6$ Hz, $J_{BX} = 8.9$ Hz, H-4 *trans* to the alkoxycarbonyl group), 2.52 (1H, part A of an ABX system, $J_{AB} = 14.3$ Hz, $J_{AX} = 9.7$ Hz, CHPh), 2.26 (1H, part B of an ABX system, $J_{AB} = 14.3$ Hz, $J_{BX} = 3.7$ Hz, CHPh); ^{13}C NMR, δ: 173.8 (s, C-5), 168.4 (s, COO), 135.2 (s, Ph), 132.0 (d, Ar), 131.8 (s, Ar), 131.6 (s, Ar), 131.1 (s, Ar), 130.7 (s, Ar), 129.8 (d, Ar), 129.7 (d, Ar), 129.0 (2d, Ph), 128.4 (2d, Ph), 128.3 (d, Ar), 127.2 (d, Ar), 126.9 (d, Ph), 125.9 (d, Ar), 125.3 (d, Ar), 125.2 (d, Ar), 124.1 (q, $^2J_{CF} = 278$ Hz, CF_3), 122.3 (d, Ar), 120.0 (s, Ar), 80.2 (d, C-2), 69.5 (q, $^2J_{CF} = 31$ Hz, $CHCF_3$), 44.3 (d, C-3), 37.0 (t, CH_2Ph), 31.6 (t, C-4); MS, *m/z*: 479 (23, M+1), 478 (61, $M^{+\cdot}$), 291 (32), 260 (27), 259 (100), 239 (23), 207 (28), 191 (19); $[\alpha]_D^{25} = +95.6$ (*c* 0.25, $CHCl_3$).

3.4.3. (1′*R*,2*S*,3*R*)-(+)-1-(9-Anthryl)-2,2,2-trifluoroethyl 2-benzyltetrahydro-5-oxo-3-furancarboxylate 11. IR ($CHCl_3$): 1786, 1766 cm^{-1}; ^{1}H NMR, δ: 8.58 (1H, s, Ar), 8.47 (1H, d, $J = 8.9$ Hz, Ar), 8.28 (1H, d, $J = 8.9$ Hz, Ar), 8.05 (1H, d, $J = 8.0$ Hz, Ar), 8.04 (1H, d, $J = 8.0$ Hz, Ar), 7.75 (1H, q, $J = 7.9$ Hz, $CHCF_3$), 7.65 (1H, t, $J = 7.7$ Hz, Ar), 7.51 (3H, m, Ar), 7.33–7.21 (5H, m, Ph), 4.88 (1H, ddd, $J_{2,3} = 7.1$ Hz, $J_{AX} = 5.3$ Hz, $J_{BX} = 5.7$ Hz, H-2, part X of an ABX system), 3.26 (1H, ddd, $J_{2,3} = 7.1$ Hz, $J_{AX} = 8.6$ Hz, $J_{BX} = 9.7$ Hz, H-3, part X of an ABX system), 3.18 (1H, part A of an ABX system, $J_{AB} = 14.6$ Hz, $J_{AX} = 5.3$ Hz, CHPh), 3.09 (1H, part B of an ABX system, $J_{AB} = 14.6$ Hz, $J_{BX} = 5.7$ Hz, CHPh), 2.70 (1H, part A of an ABX system, $J_{AB} = 17.9$ Hz, $J_{AX} = 8.6$ Hz, H-4 *cis* to the alkoxycarbonyl group), 2.52 (1H, part B of an ABX system, $J_{AB} = 17.6$ Hz, $J_{BX} = 9.7$ Hz, H-4 *trans* to the alkoxycarbonyl group); ^{13}C NMR, δ: 173.4 (s, C-5), 169.1 (s, COO), 134.4 (s, Ph), 131.8 (d, Ar), 131.7 (s, Ar), 131.6 (s, Ar), 131.1 (s, Ar), 130.4 (s, Ar), 129.8 (2d, Ph), 129.7 (s, Ar), 129.6 (s, Ar), 128.8 (2d, Ph), 128.1 (d, Ar), 127.4 (d, Ph), 126.8 (d, Ar), 125.5 (d, Ar), 125.2 (d, Ar), 125.1 (d, Ar), 124.0 (q, $^1J_{CF} = 290$ Hz, CF_3), 122.1 (d, Ar), 119.9 (s, Ar), 81.0 (d, C-2), 69.9 (q, $^2J_{CF} = 33$ Hz, $CHCF_3$), 43.8 (d, C-3), 40.2 (t, CH_2Ph), 31.5 (t, C-4); MS, *m/z*: 479 (30, M+1), 478 (100, $M^{+\cdot}$), 291 (27), 259 (91), 239 (25), 207 (91), 191 (12); $[\alpha]_D^{25} = +7.7$ (*c* 0.13, $CHCl_3$).

3.4.4. (1′*S*,2*S*,3*R*)-(−)-1-(9-Anthryl)-2,2,2-trifluoroethyl 2-benzyltetrahydro-5-oxo-3-furancarboxylate 12. IR ($CHCl_3$): 1786, 1766 cm^{-1}; ^{1}H NMR, δ: 8.60 (1H, s, Ar), 8.56 (1H, d, $J = 8.9$ Hz, Ar), 8.28 (1H, d, $J = 8.9$ Hz, Ar), 8.06 (2H, 2d, $J = 8.4$ Hz, Ar), 7.79 (1H, q, $J = 7.9$ Hz, $CHCF_3$), 7.65 (1H, t, $J = 7.7$ Hz, Ar), 7.52 (3H, m, Ar), 7.09 (3H, m, Ph), 7.02 (2H, m, Ph), 4.73 (1H, ddd, $J_{2,3} = 7.0$ Hz, $J_{AX} = 6.1$ Hz, $J_{BX} = 4.7$ Hz, H-2, part X of an ABX system), 3.28 (1H, part X of an ABX system, $J_{2,3} = 7.0$, $J_{AX} = 9.5$, $J_{BX} = 4.7$, H-3), 3.03 (1H, part A of an ABX system, $J_{AB} = 14.3$ Hz, $J_{BX} = 4.7$ Hz, CHPh), 2.94 (1H, part B of an ABX system, $J_{AB} = 14.3$ Hz, $J_{AX} = 6.1$ Hz, CHPh), 2.84 (1H, part A of an ABX system, $J_{AB} = 17.9$ Hz, $J_{AX} = 8.4$ Hz, H-4 *cis* to the alkoxycarbonyl group), 2.60 (1H, part B of an ABX system, $J = 17.9$ Hz, $J_{BX} = 9.5$ Hz, H-4 *trans* to the alkoxycarbonyl group); ^{13}C NMR, δ: 173.5 (s, C-5), 169.4 (s, COO), 134.4 (s, Ph), 131.9 (d + s, Ar), 131.6 (s, Ar), 131.2 (s, Ar), 130.6 (s, Ar), 129.8 (d, Ar), 129.7 (2d, Ph), 128.7 (2d, Ph), 128.2 (d, Ar), 127.3 (d, Ph), 127.0 (d, Ar), 125.8 (d, Ar), 125.3 (2d, Ar), 124.1 (q, $^1J_{CF} = 292$ Hz, CF_3), 122.2 (d, Ar), 120.1 (s, Ar), 81.0 (d, C-2), 69.9 (q, $^2J_{CF} = 35$ Hz, $CHCF_3$), 44.2 (d, C-3), 40.4 (t, CH_2Ph), 31.9 (t, C-4); MS, *m/z*: 479 (10, M+1), 478 (36, $M^{+\cdot}$), 291 (9), 260 (18), 259 (100), 239 (27), 208 (32), 207 (87), 193 (10), 191 (10), 179 (14); $[\alpha]_D^{25} = -22.5$ (*c* 0.40, $CHCl_3$).

3.4.5. (1′*R*,2*S*,3*S*)-(−)-1-(9-Anthryl)-2,2,2-trifluoroethyl 2-methyltetrahydro-5-oxo-3-furancarboxylate 15. IR ($CHCl_3$): 1786, 1766 cm^{-1}; ^{1}H NMR, δ: 8.60 (1H, d, $J = 8.9$ Hz, Ar), 8.59 (1H, s, Ar), 8.34 (1H, d, $J = 8.9$ Hz, Ar), 8.05 (1H, d, $J = 8.4$ Hz, Ar), 8.03 (1H, d, $J = 8.0$ Hz, Ar), 7.90 (1H, q, $J = 8.0$ Hz, $CHCF_3$), 7.64 (2H, m, Ar), 7.52 (1H, t, $J = 8.4$ Hz, Ar), 7.50 (1H, t, $J = 8.4$ Hz, Ar), 4.76 (1H, quintet, $J = 6.6$ Hz, H-2), 3.63 (1H, ddd, $J_{2,3} = 6.6$ Hz, $J_{AX} = 9.1$ Hz, $J_{BX} = 7.1$ Hz, H-3, part X of an ABX system), 2.90 (1H, part A of an ABX system, $J_{AB} = 17.6$ Hz, $J_{AX} = 9.1$ Hz, H-4 *cis* to the alkoxycarbonyl group), 2.70 (1H, part B of an ABX system, $J_{AB} = 17.6$ Hz, $J_{BX} = 7.1$ Hz, H-4 *trans* to the alkoxycarbonyl group), 0.83 (3H, d, $J = 6.6$ Hz, CH_3); ^{13}C NMR, δ: 174.2 (s, C-5), 168.5 (s, COO), 131.9 (d, Ar), 131.7 (s, Ar), 131.6 (s, Ar), 131.1 (s, Ar), 130.6 (s, Ar), 129.7 (d, Ar), 129.6 (d, Ar), 128.2 (d, Ar), 127.0 (d, Ar), 125.9 (d, Ar), 125.3 (2d, Ar), 124.2 (q, $^1J_{CF} = 271$, CF_3), 122.3 (d, Ar), 120.1 (s, Ar), 76.0 (d, C-2), 69.5 (q, $^2J_{CF} = 35$ Hz, $CHCF_3$), 44.8 (d, C-3), 31.2 (t, C-4), 16.2 (q, CH_3); MS, *m/z*: 403 (19, M+1), 402 (77, $M^{+\cdot}$), 333 (4, M−CF_3), 259 (53), 239 (17), 207 (100), 179 (12); $[\alpha]_D^{25} = -72.6$ (*c* 0.72, $CHCl_3$).

3.4.6. (1′*S*,2*S*,3*S*)-(−)-1-(9-Anthryl)-2,2,2-trifluoroethyl 2-methyltetrahydro-5-oxo-3-furancarboxylate 16. IR ($CHCl_3$): 1786, 1766 cm^{-1}; ^{1}H NMR, δ: 8.60 (1H, d, $J = 7.7$ Hz, Ar), 8.59 (1H, s, Ar), 8.34 (1H, d, $J = 9.1$ Hz, Ar), 8.05 (1H, d, $J = 8.0$ Hz, Ar), 8.04 (1H, d, $J = 7.3$ Hz, Ar), 7.87 (1H, q, $J = 8.0$ Hz, $CHCF_3$), 7.66 (1H, t, $J = 7.8$ Hz, Ar), 7.60

(1H, t, $J = 7.3$ Hz, Ar), 7.53 (1H, t, $J = 6.2$ Hz, Ar), 7.51 (1H, t, $J = 7.1$ Hz, Ar), 4.96 (1H, quintet, $J = 6.6$ Hz, H-2), 3.59 (1H, ddd, $J_{2,3} = 6.6$ Hz, $J_{AX} = 7.0$ Hz, $J_{BX} = 9.4$ Hz, H-3, part X of an ABX system, H-3), 2.87 (1H, part A of an ABX system, $J_{AB} = 17.6$ Hz, $J_{AX} = 9.4$ Hz, H-4 *cis* to the alkoxycarbonyl group), 2.61 (1H, part B of an ABX system, $J_{AB} = 17.6$ Hz, $J_{BX} = 7.0$ Hz, H-4 *trans* to the alkoxycarbonyl group), 1.36 (3H, d, $J = 6.6$ Hz, CH_3); ^{13}C NMR, δ: 174.2 (s, C-5), 168.6 (s, COO), 131.9 (d, Ar), 131.8 (s, Ar), 131.5 (s, Ar), 131.1 (s, Ar), 130.7 (s, Ar), 129.8 (d, Ar), 129.6 (d, Ar), 128.2 (d, Ar), 127.0 (d, Ar), 125.9 (d, Ar), 125.3 (2d, Ar), 124.2 (q, $^1J_{CF} = 278$ Hz, CF_3), 122.2 (d, Ar), 120.2 (s, Ar), 76.0 (d, C-2), 69.7 (q, $^2J_{CF} = 35$ Hz, *C*HCF$_3$), 44.4 (d, C-3), 31.1 (t, C-4), 16.7 (q, CH_3); MS, *m*/*z*: 403 (13, M+1), 402 (53, M$^{+\cdot}$), 333 (2, M−CF$_3$), 259 (39), 239 (11), 207 (100), 179 (13); $[\alpha]_D^{25} = -36.3$ (*c* 0.60, $CHCl_3$).

3.4.7. (1′*R*,2*S*,3*R*)-(−)-1-(9-Anthryl)-2,2,2-trifluoroethyl 2-methyltetrahydro-5-oxo-3-furancarboxylate 17. IR ($CHCl_3$): 1786, 1766 cm^{-1}; ^{1}H NMR, δ: 8.60 (1H, s, Ar), 8.58 (1H, d, $J = 8.9$ Hz, Ar), 8.32 (1H, d, $J = 8.9$ Hz, Ar), 8.05 (1H, d, $J = 8.4$ Hz, Ar), 8.04 (1H, d, $J = 8.4$ Hz, Ar), 7.83 (1H, q, $J = 7.9$ Hz, CHCF$_3$), 7.67 (1H, t, $J = 7.7$ Hz, Ar), 7.59 (1H, t, $J = 7.7$ Hz, Ar), 7.52 (2H, m, Ar), 4.69 (1H, dq, $J_{2,3} = 8.0$ Hz, $J_{2,Me} = 6.2$ Hz, H-2), 3.19 (1H, dt, $J_{2,3} = 8.0$ Hz, $J_{AX} = 9.5$ Hz, $J_{BX} = 9.5$ Hz, H-3, part X of an ABX system, H-3), 2.79 (1H, part A of an ABX system, $J_{AB} = 17.9$ Hz, $J_{AX} = 9.5$ Hz, H-4 *cis* to the alkoxycarbonyl group), 2.77 (1H, part B of an ABX system, $J_{AB} = 17.9$ Hz, $J_{BX} = 9.5$ Hz, H-4 *trans* to the alkoxycarbonyl group), 1.60 (3H, d, $J = 6.2$ Hz, CH_3); ^{13}C NMR, δ: 173.5 (s, C-5), 169.0 (s, COO), 131.9 (d, Ar), 131.8 (s, Ar), 131.5 (s, Ar), 131.1 (s, Ar), 130.6 (s, Ar), 129.8 (d, Ar), 129.7 (d, Ar), 128.2 (d, Ar), 127.0 (d, Ar), 125.6 (d, Ar), 125.3 (2d, Ar), 124.1 (q, $^1J_{CF} = 284$ Hz, CF_3), 122.2 (d, Ar), 120.0 (s, Ar), 77.6 (d, C-2), 70.1 (q, $^2J_{CF} = 35$ Hz, *C*HCF$_3$), 47.3 (d, C-3), 32.2 (t, C-4), 20.8 (q, CH_3); MS, *m*/*z*: 403 (21, M+1), 402 (99, M$^{+\cdot}$), 333 (5, M−CF$_3$), 259 (64), 239 (21), 238 (18), 208 (18), 207 (100), 191 (12), 189 (10), 179 (16); $[\alpha]_D^{25} = -8.5$ (*c* 0.20, $CHCl_3$).

3.4.8. (1′*S*,2*S*,3*R*)-(−)-1-(9-Anthryl)-2,2,2-trifluoroethyl 2-methyltetrahydro-5-oxo-3-furancarboxylate 18. IR ($CHCl_3$): 1786, 1766 cm^{-1}; ^{1}H NMR, δ: 8.60 (1H, d, $J = 8.9$ Hz, Ar), 8.59 (1H, s, Ar), 8.34 (1H, d, $J = 8.9$ Hz, Ar), 8.05 (2H, 2d, $J = 8.4$ Hz, Ar), 7.86 (1H, q, $J = 7.7$ Hz, CHCF$_3$), 7.67 (1H, t, $J = 7.7$ Hz, Ar), 7.60 (1H, t, $J = 7.7$ Hz, Ar), 7.53 (2H, m, Ar), 4.53 (1H, dq, $J_{2,3} = 7.3$ Hz, $J_{2CH_3} = 6.2$ Hz, H-2), 3.20 (1H, ddd, $J_{2,3} = 7.3$ Hz, $J_{AX} = 8.3$ Hz, $J_{BX} = 9.0$ Hz, H-3, part X of an ABX system, H-3), 2.96 (1H, part A of an ABX system, $J_{AB} = 17.9$ Hz, $J_{AX} = 8.3$ Hz, H-4 *cis* to the alkoxycarbonyl group), 2.89 (1H, part B of an ABX system, $J_{AB} = 17.9$ Hz, $J_{BX} = 9.0$ Hz, H-4 *trans* to the alkoxycarbonyl group), 1.41 (3H, d, $J = 6.2$ Hz, CH_3); ^{13}C NMR, δ: 173.6 (s, C-5), 169.2 (s, COO), 131.9 (d, Ar), 131.8 (s, Ar), 131.6 (s, Ar), 131.1 (s, Ar), 130.5 (s, Ar), 129.8 (d, Ar), 129.7 (d, Ar), 128.2 (d, Ar), 126.9 (d, Ar), 125.8 (d, Ar), 125.3 (d, Ar), 125.2 (d, Ar), 124.1 (q, $^1J_{CF} = 278$ Hz, CF_3), 122.2 (d, Ar), 120.1 (s, Ar), 77.7 (d, C-2), 70.0 (q, $^2J_{CF} = 35$ Hz, *C*HCF$_3$), 47.2 (d, C-3), 32.1 (t, C-4), 20.9 (q, CH_3). MS, *m*/*z*: 403 (21, M+1), 402 (86, M$^{+\cdot}$), 333 (5, M−CF$_3$), 259 (53), 239 (18), 208 (31), 207 (100), 179 (14); $[\alpha]_D^{25} = -1.9$ (*c* 0.26, $CHCl_3$).

3.5. 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;[19] 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 semiempirical calculation using the AM1 Hamiltonian[16] as implemented in Sybyl6.8[20] (Sybyl6.8, Tripos Inc., 1699 South Hanley Road, St. Louis, MO 63144, USA). 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.

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