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Synthesis, characterization and assignment of the absolute configuration of 4,4-dimethyl-5-oxo-tetrahydrofuran-3-carboxylic acid and its esters: a combined experimental and theoretical investigation

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ABSTRACT

The synthesis of a new, optically active, paraconic-acid derivative 4,4-dimethyl-5-oxo-tetrahydrofuran-3-carboxylic acid and its methyl and ethyl esters was accomplished by a procedure involving the kinetic enzymatic resolution of the racemic ethyl ester. Thus, ethyl (+)-4,4-dimethyl-5-oxo-tetrahydrofuran-3-carboxylate, derived from a ring fission, was isolated at low conversion values, with 94% ee using HLAP as the enzymatic source. The corresponding enantiomerically pure acid was also obtained.
The absolute configuration of the products was determined based on the results of an extensive computational study of the specific rotation of the acid and methyl ester. Four different wavelengths were considered and comparisons with the sign and magnitude of the corresponding experimental observations were carried out. Solvent effects on both the conformational space and the specific rotation were included in the computations using the Polarizable Continuum Model.
The assigned absolute configuration of the title compounds is (*R*)-(+), which is in agreement with a tentative experimental assignment based on an analysis of the circular dichroism curves.

1. Introduction

The γ-butyrolactone skeleton is present in many natural products, and functionalization at the heterocyclic ring defines different classes of compounds. Paraconic acids constitute as a group of highly substituted β-carboxylated-γ-butyrolactones which exhibit biological activity such as antitumour and antibiotic properties and are usually α- and γ-disubstituted,[1] bearing an alkyl chain at the γ-position and a methyl[1e,2] or a methylene group at the α-position.[1f,g]

The β-carboxylic group of the paraconic acids could also be transformed into a hydroxymethyl group leading to another class of compounds that are known to be involved in the production of secondary metabolites such as antibiotics. A-factor,[3] factor I,[4] factors from *Streptomyces bikiniensis* and *Streptomyces cyaneofuscatus* and virginiae butanolides[5] from *Streptomyces virginiae*, are examples of dihydro-5-alkyl-4-hydroxymethyl-2(3H)-furanones which all induce the production of different antibiotics.

As a result of the biological activity found and their versatility as building blocks, many reports have appeared in the literature which propose the synthesis of both racemic and enantiomerically pure natural paraconic acids derivatives as well as non-natural ones. In our laboratory, we have recently synthesized non-natural paraconic acids such as terebic acid,[6] 2-methyl[6] and 4-methylparaconic acids[7] and 2-benzylparaconic acid[8] in optically active form, as it is well known that biological activity depends on the absolute configuration (AC) of the chiral compound.

We now focus our attention on the chemoenzymatic synthesis of the newly formed 4,4-dimethyl-5-oxo-tetrahydrofuran-3-carboxylic acid and its methyl and ethyl esters, whose absolute configuration is assigned by ab initio investigations of their specific rotation. The molecular formulae of the novel compounds are shown in Figure 1 and are labelled **1**, **2** and **3**, respectively.

As for any other natural or newly synthesized optically active species, the assignment of the absolute configuration of these new derivatives is an important step in their chemical characterization. Several methods can be used in the assignment of the AC but their applicability is not always so simple. Experimentally, the AC assignment is, in general, an elaborate process, due to the lack of an immediate, or intuitive, correspondence between the measured chiroptical response and the absolute configuration of the chiral molecule. One can compare the electronic circular dichroism (ECD) spectrum with structurally similar molecules with the same stereogenic centres, use empirical rules to determine the

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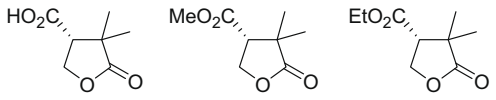


(+)-**1** (+)-**2** (+)-**3**

Figure 1. 4,4-Dimethylparaconic acid 1, methyl 4,4-dimethylparaconate 2 and ethyl 4,4-dimethylparaconate **3**.

sign of its specific rotation, or, if possible, convert the product to a molecule of known AC.[9] If the molecule of unknown AC contains a heavy atom[10] and crystallizes, its AC can also be determined using X-ray crystallography.[11,12] Recently, NMR spectroscopy was applied in the assignment of the absolute configuration of several compounds, based on the derivatization of the substrate with the two enantiomers of a chiral derivatizing agent, producing two diastereomeric derivatives. This methodology has received great attention and several empirical rules have been formulated in the literature; more recently theoretical calculations of structure and energy have supported these theories giving more reliability to the absolute configuration assignment process.[8,13]

One alternative method for assigning the absolute configuration of the chiral species is by theoretical calculations. The specific rotation (or rotatory power) is computed for a given enantiomer in a configuration chosen a priori, and then compared, in terms of both sign and magnitude, with the specific rotation values measured experimentally.[9,14] In addition, one could also computationally simulate the electronic (ECD) or/and the vibrational circular dichroism (VCD) spectrum of the given chiral compound and compare it/them to the corresponding experimental spectrum,[15] as carried out, for instance, by Stephens et al. for the natural products quadrone[16] and schizozygine,[17] as well as for other organic molecules.[18] Indeed, it can be argued that the combined use of experimental and computational VCD data to assign the AC of chiral compounds is nowadays one of the most reliable approaches for AC assignment, but, as also reported by Giorgio et al. in a recent publication,[19] it is still limited by the availability of a rather expensive instrument and by the amount of sample required for the measurement of the spectrum. Experimental specific rotation data can, on the other hand, be easily collected with a rather inexpensive polarimeter, which can be found in most organic chemistry laboratories.

The reliability of the results obtained by theoretical calculations is obviously related to the accuracy one can expect from the chosen computational method, and to the extent all factors that might influence the final result have been accounted for. The increase of publications on both theoretical and applicative aspects[14h,i,20] related to the determination of chiroptical properties in the recent years is a proof of the success of the computational strategy for the AC assignment. At the same time it has supplied a sufficient amount of 'statistical data' to allow for an assessment of the strengths and the limitations of the currently available computational approaches.

For rigid molecules, it is nowadays generally established that values of specific rotations as accurate as ±30 (in units of 10^{-1} deg cm^2 g^{-1}) can be obtained if the molecular geometry is optimized at the DFT/B3LYP[21] level using a basis set of (at least) 6-31G** quality, and the specific rotations are determined using time-dependent (TD)-DFT/B3LYP and a basis set of (at least) aug-cc-pVDZ quality.[14h,20,22,23]

As specific rotation measurements are in most cases performed in solution, solvent effects should be taken into account in the calculations for a consistent comparison with experimental results.[24,25] Even though the role of the solvent can be negligible in many cases, there are instances where it becomes dominant or even where the neglect of solvent effects can lead to a completely wrong conclusion concerning the AC of the system investigated.[7,26] A rather successful approach to include solvent effects in specific rotation calculations is via the so-called 'polarizable continuum model' (PCM).[25,27] The solvent is described by a polarizable continuum, which surrounds the solute molecule(s), and the solute is placed in the dielectric medium inside a cavity modelled after its shape and composed of interlocking spheres centred on each atom or on functional groups.

As novel derivatives of paraconic acid, the title compounds of our investigation are expected to possess a relatively high degree of conformational freedom. This complicates further the computational simulation, since the total specific rotation will result from the weighted average of the specific rotation for each conformer. A conformational search has to be first carried out in order to identify all statistically significant conformers and their population fractions, and the specific rotation calculations have to be repeated for each of these conformers. Moreover, if the solvent description is to be included, it is important to recognize that it can affect the specific rotation in two ways, namely by modifying the population fractions of the conformers in the geometry optimization process (solvent 'relaxation' effect) and by modifying the value of the specific rotation compared to that in vacuo.

2. Results and discussion

2.1. Experimental approach

2.1.1. Synthesis of substrates

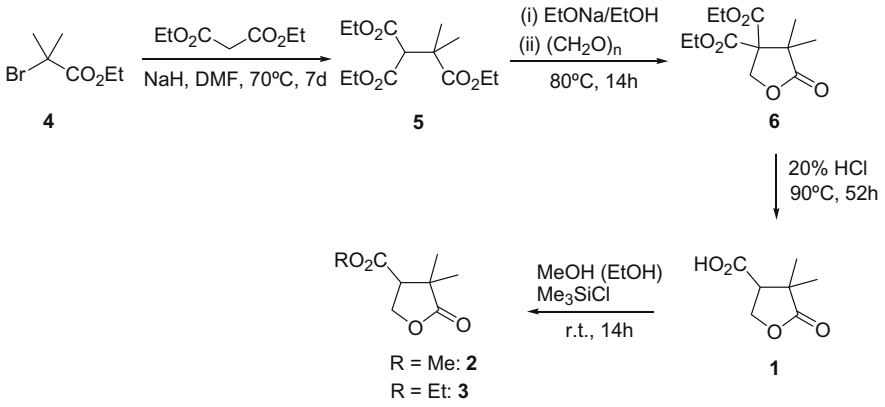
Chiral racemic lactones **2** and **3** were synthesized following a modified literature procedure,[7] from ethyl 2-bromo-2-ethylpropionate **4** and diethylmalonate (Scheme 1). The resulting intermediate **5** was treated with paraformaldehyde to afford the corresponding lactone **6**, from which lactonic acid **1** was obtained by hydrolysis and decarboxylation on prolonged heating in acidic solution. Its esterification with methanol or ethanol in the presence of trimethylsilyl chloride[28] gave the corresponding lactonic esters **2** and **3**, respectively. The overall yield was around 60% in both cases. The lactonic esters were purified using column chromatography, characterized spectroscopically and then were subjected to enzymatic resolution.

2.1.2. Enzymatic hydrolyses

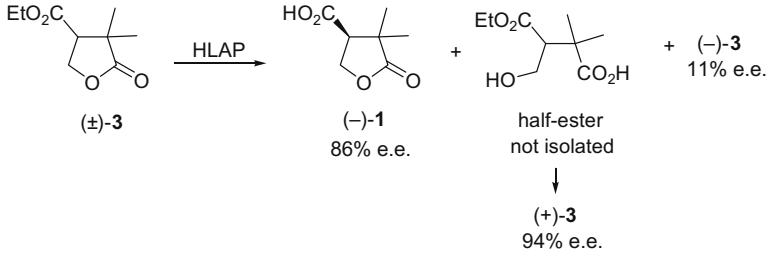
The enzymatic hydrolyses were performed on lactonic ester **3** using a series of commercially available enzymes, namely porcine pancreatic lipase (PPL), lipase from *Pseudomonas species* (PS), lipase from *Pseudomonas fluorescens* (AK), *Candida cylindracea* lipase (CCL), *Aspergillus niger* (AP12), 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 proteases from *Bacillus subtilis*. The hydrolytic reactions were monitored by a pH-STAT instrument with the addition of 1 M NaOH.

Unfortunately, the hydrolyses were not regioselective and both alkoxycarbonyl and lactone groups were hydrolyzed simultaneously, leading to mixtures of products (Scheme 2). A further complication was the cyclization of the hydroxy half ester, resulting from hydrolytic opening of the heterocycle, occurring during the acidic work-up, with the subsequent formation of the optically active parent molecule. Therefore, in order to have a thorough understanding of the outcome of the reaction, an accurate work-up had to be carried out (see Section 4).

Of all the enzymes used HLAP and PLAP were the most efficient at low conversion values. HLAP gave, after 10 min, the lactone from ring fission (+)-**3** with 94% ee in an admixture with the lactonic acid (−)-**1** with 86% ee in a 3:2 ratio, respectively. The unreacted ester (−)-**3** had 11% ee (Scheme 2). PLAP gave, after 68 min, the lac-



Scheme 1. Synthesis of substrates **2** and **3**.



Scheme 2. Enzymatic resolution of lactonic ester **3**.

tone from ring fission (+)-**3** with 94% ee in admixture with the lactonic acid (+)-**1** having 28% ee in 85:15 ratio. The unreacted ester (−)-**3** had 26% ee. The negative sign of the unreacted ester **3** was determined by the amount of ring fission product (+)-**3**. The lactonic acid (+)-**1** with 94% ee was obtained by chemical hydrolysis with HCl at reflux of the ethyl ester (+)-**3** with the same enantiomeric excess. Esterification of (+)-**1** with diazomethane afforded the corresponding methyl ester (+)-**2** with 94% ee.

Table 1 reports the most significant UV and CD spectroscopic data for compounds (+)-**1**, (+)-**2** and (+)-**3**, in two different solvents (methanol and acetonitrile), together with their specific rotation values.

Table 1
Specific rotation, UV and CD experimental data for compounds (*R*)-(+)-**1**, (*R*)-(+)-**2** and (*R*)-(+)-**3**

Compound	Solvent	$[\alpha]^{25}_{589}$ (*c*, g/100 mL)	UV data λ_{max} (ε_{max})	CD data $\Delta\varepsilon$ (λ)
(+)-**1**	MeOH	+12.9 (0.31)	212 (135) 222[a] (110)	+0.85 (214)
(+)-**1**	MeCN	+16.4 (0.25)	201 (157) 214[a] (152)	+0.86 (215)
(+)-**2**	MeOH	+20.4 (0.25)	210 (206) 213[a] (201)	+0.80 (213)
(+)-**2**	MeCN	+18.4 (0.25)	202 (243) 217[a] (184)	+0.80 (213)
(+)-**3**	MeOH	+16.7 (0.4)	213 (168)	+1.02 (213)
(+)-**3**	MeCN	+18.1 (0.37)	210 (149) 217 (146)	+1.03 (213)

Enantiomeric excess 94%.
[a] Shoulder.

In Table 2 the specific rotation values at different wavelengths and in different solvents are listed.

It is important to note that according to the data collected in Tables 1 and 2, the experimental results obtained in the protic solvent methanol are similar to those collected in the aprotic solvent acetonitrile. In our opinion, this is an indication that the protic nature of the solvent has a very limited effect on the specific rotation values, that is, that H-bond effects between the solvent and the solute can be expected to not play a significant role.

Table 2
Experimental specific rotation at five different wavelengths for compounds (+)-**1**, (+)-**2** and (+)-**3** in various solvents

Compound	Solvent	*c*, g/100 mL	$[\alpha]^{25}_{589}$	$[\alpha]^{25}_{578}$	$[\alpha]^{25}_{546}$	$[\alpha]^{25}_{436}$	$[\alpha]^{25}_{365}$
(+)-**1**	$CHCl_3$	0.68	+8.2	+9.0	+10.4	+17.6	+29.4
(+)-**1**	MeOH	0.31	+12.9	+13.5	+15.5	+27.1	+44.2
(+)-**1**	MeCN	0.25	+16.4	+16.8	+19.2	+32.8	+53.2
(+)-**2**	$CHCl_3$	0.32	+16.6	+17.5	+19.7	+33.4	+49.4
(+)-**2**	MeOH	0.25	+20.4	+20.8	+23.6	+39.6	+57.6
(+)-**2**	MeCN	0.25	+18.4	+19.6	+21.2	+37.2	+56.4
(+)-**2**	C_6H_{12}	0.13	+6.2	+6.2	+7.7	+14.6	+23.8
(+)-**3**	$CHCl_3$	0.45	+11.3	+12.2	+13.8	+24.0	+37.3
(+)-**3**	MeOH	0.40	+16.7	+17.5	+19.8	+34.2	+54.2
(+)-**3**	MeCN	0.37	+18.1	+19.2	+21.9	+37.3	+59.4
(+)-**3**	C_6H_{12}	0.14	+3.6	+3.6	+5.7	+7.1	+12.1

Enantiomeric excess 94%.

2.1.3. Circular dichroism analysis

The CD spectra of the 4,4-dimethylparaconic acid (+)-**1** and its methyl ester (+)-**2** have been compared with the analogous non-methylated compounds, namely paraconic acid (+)-**7** and its methyl ester (+)-**8**, whose absolute configurations have been already assessed.[3c,6,29] Optimization of the geometry in methanol solution at the DFT/B3LYP level (vide infra) established that the major conformers of (+)-**1** and (+)-**7** have the same lactone ring conformation,[26c] which is responsible for the positive Cotton effect in the CD curves reported in Figure 2. Since the two lactones have the same lactone ring conformation, it seems correct to compare the CD curves of (+)-**1** and (*R*)-(+)-**7** in the assignment of the

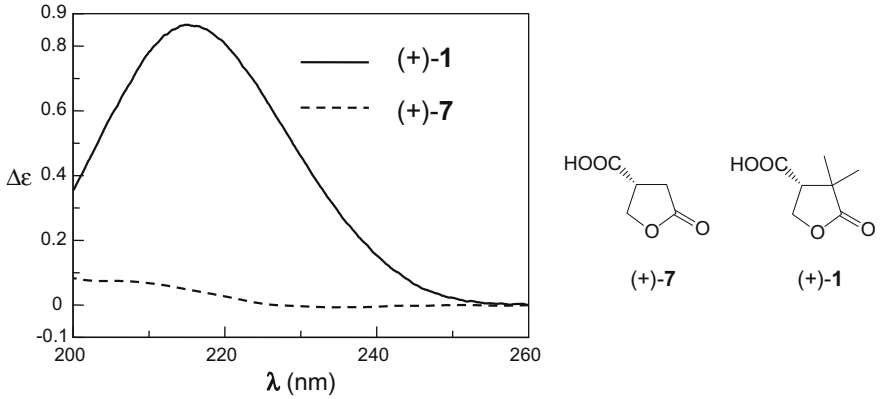


Figure 2. CD spectra of (+)-1 and (+)-7. $\Delta\varepsilon$ is expressed in $cm^2\ mmol^{-1}$.

absolute configuration of (+)-**1**, although their magnitudes are considerably different [this is partially due to the different enantiomeric excess: 94% for (+)-**1** and 80% for (+)-**7**]. In spite of this difference we assign the same (*R*) configuration to (+)-**1**.

The CD curves of the corresponding methyl esters (*R*)-(+)-**8** and (+)-**2**, which have almost the same ee's [94% ee for (+)-**2** and 92% ee for (+)-**8**] show a positive Cotton effect, despite the difference in magnitude, thus suggesting that the conformation of the lactone ring is again the same (Fig. 3).

2.2. Computational approach

2.2.1. Definitions and computational details

The specific rotation $[\alpha]_\lambda$ (at a given wavelength λ) of a molecule possessing *Nc* conformers can be written

$$[\alpha]_\lambda = \sum_{i=1}^{N_C} X_i [\alpha]_\lambda^i = \sum_{i=1}^{N_C} [\alpha]_\lambda^{i,w} \quad (1)$$

where $[\alpha]_\lambda^i$ and X_i are the specific rotation and the population fraction of the *i*-th conformer, respectively. From Boltzmann's statistics

$$X_i = \frac{\exp(-\Delta_i E/kT)}{\sum_{i=1}^{N_C} \exp(-\Delta_i E/kT)} \quad (2)$$

where $\Delta_i E = E_i - E_1$ is the energy difference between the *i*-th conformer and the most stable one, whose energy is here indicated by E_1; *k* is the Boltzmann constant and *T* is the temperature.

From the definition given above, we observed that in order to determine the specific rotation of our flexible systems we need to: (1) carry out a conformational search in order to determine the structure and energy of all stable conformers; (2) compute the specific rotation of each conformer and (3) add up all calculated specific rotation values, each weighted by the population fraction of the corresponding conformer to obtain the total specific rotation. Due to the weighting procedure, the accuracy in the determination of molecular geometries and relative energies plays a key role in assessing the reliability of the total specific rotation. It can be seen that the results are very sensitive to the energetics and that the convergence to local minima is a difficult task, in particular for molecules with stable structures very close in energy. Even a rather small change in the energy of the conformers can, in principle induce significant changes in the population fractions and consequently in the weighted optical rotations. To find the stable conformers we followed a strategy similar to the one adopted previously for other paraconic acid derivatives.[7,26c,30] We selected a certain number of initial conformations for each molecule by varying the dihedral angles describing the five-membered ring puckering (two positions, up and down) and the carboxylic group torsional motion (three positions). Since compounds **1**, **2** and **3** have the same absolute configuration, we limited the analysis to the acid and the methyl ester, due to the increase in the number of conformers that would be obtained for the ethyl ester because of the additional torsional motion of the ethyl group. The absolute configuration of the selected initial conformers was chosen as (*R*).

The geometry of each form was then fully optimized at the DFT level using the B3LYP functional and the aug-cc-pVDZ basis set. Solute-solvent interactions were included during the geometry optimization via the PCM.[26b] A dielectric constant of ε =32.630 was used to describe the methanol solvent in the continuum model. The interlocking spheres used to build the molecule-shaped cavity were centred on the heavy atoms (C, O) of the molecule(s) with radii chosen according to the United Atom Topological Model.[31]

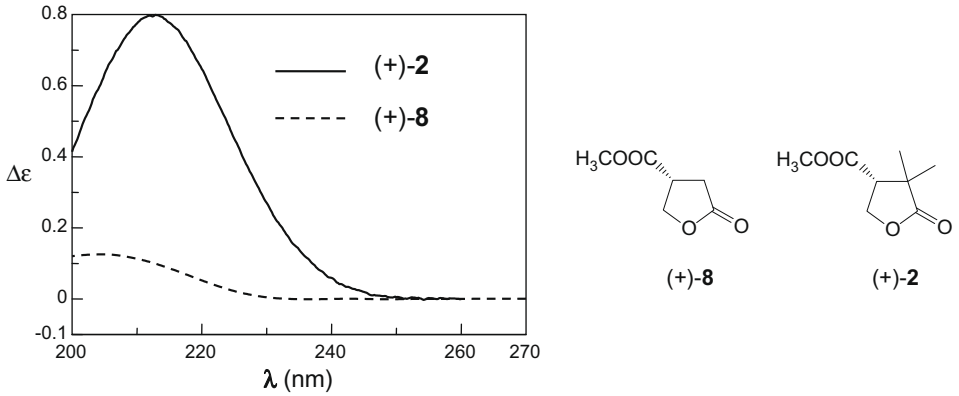


Figure 3. CD spectra of (+)-**2** and (+)-**8**. $\Delta\varepsilon$ is expressed in $cm^2\ mmol^{-1}$.

The optimization procedure, repeated both in vacuo and in methanol, led to the identification of four minima for both molecular species. For the solvated case, the final structures are shown in Figures 4 and 5. The in vacuo structures are similar to the solvated ones and have been omitted.

The specific rotation of each stable structure was calculated, in vacuo and in solution, at the TD-DFT level of theory using the B3LYP functional and the aug-cc-pVDZ basis set. Gauge-invariant atomic orbitals (GIAOs) were employed to guarantee origin-independent specific rotation values. The solvent effect in this case was accounted for by the PCM, employing the same values for the cavity radii as used in the geometry optimization. A non-equilibrium solvation scheme was applied in the calculations of the direct solvent effects on the calculated specific rotation,[32] using both the static and optical ($\varepsilon_\infty = 1.7580$) dielectric constants of the solvent.

For all species the specific rotation was calculated at four different wavelengths, 589.3 nm (the sodium D-line), 578.0 nm, 546.0 nm and 436.0 nm, which correspond to 4 of the 5 wavelengths accessible to our polarimeter. Calculations were not undertaken at the lowest wavelength (365 nm) as this wavelength was considered to be too close to the absorptive region of the sample. All calculations were performed with a local version of the DALTON 2.0 program,[33] containing the PCM modules of Ref. 34 Figures 4 and 5 were generated using Jmol.[35]

It could be argued that the choice of methanol as solvent is not the most appropriate, since it may give rise to H-bond formations with the solute. However, as already pointed out in Section 2.1.2, we do not expect H-bonds to play a significant role on the structural properties and specific rotation of the given species, since the experimental results obtained in methanol are very similar to those obtained in the aprotic solvent acetonitrile for all wavelengths. As further confirmation of such an assumption, we also carried out a full conformational investigation and specific rotation study at all frequencies of the acid in acetonitrile ($\varepsilon = 36.64$). The results were completely analogous with those obtained in methanol and have been omitted for the sake of conciseness.

2.2.2. Discussion of the computational results

All results obtained in vacuo and in methanol for the energetics of both molecules are collected in Table 3. The first column lists the conformers; the next two columns report the energy differences (in kcal/mol) with respect to the conformer with the lowest energy, and the corresponding relative populations (in percentage, $X_i \times 100$, $T = 298.15$ K) for the in vacuo case. Corresponding data in methanol are given in the next two columns.

Table 3
Molecules **1** and **2**.

Conf.	In vacuo		In methanol	
	$\Delta_i E$	$X_i \times 100$	$\Delta_i E$	$X_i \times 100$
1A	0.0000	81.21	0.0000	58.77
1B	1.2041	10.64	0.8862	13.17
1C	1.5894	5.55	0.7256	17.27
1D	2.0396	2.60	1.0043	10.79
2A	0.0000	78.39	0.0000	59.84
2B	1.0840	12.58	0.9516	12.01
2C	1.5424	5.80	0.6703	19.30
2D	1.8892	3.23	1.1324	8.85

Relative energies ($\Delta_i E$, kcal/mol) and population fractions (X_i,%), in vacuo and in methanol for the conformers optimized in vacuo and methanol, respectively. Population fractions refer to $T = 298.15$ K.

The specific rotation data are collected in Tables 4 and 5 for acid **1** and ester **2**, respectively. At each wavelength, the absolute specific rotations ($[\alpha]^i_\lambda$) of each conformer and the weighted specific rotation $[\alpha]^{i,w}_\lambda = [\alpha]^i_\lambda \times X_i$ are given. The sum of all the weighted $[\alpha]^{i,w}_\lambda$ (at a given λ) gives the total specific rotation $[\alpha]_\lambda$. For the solvated case, the latter is directly comparable with the experimental results.

Starting with an analysis of the geometry relaxation effects from vacuo to condensed phase, we also report a comparison of the variations in the conformational (percentage) population fractions in Figure 6.

The effect of the solvent is noticeable and basically is the same for both systems: conformer A is slightly destabilized, in favour of a

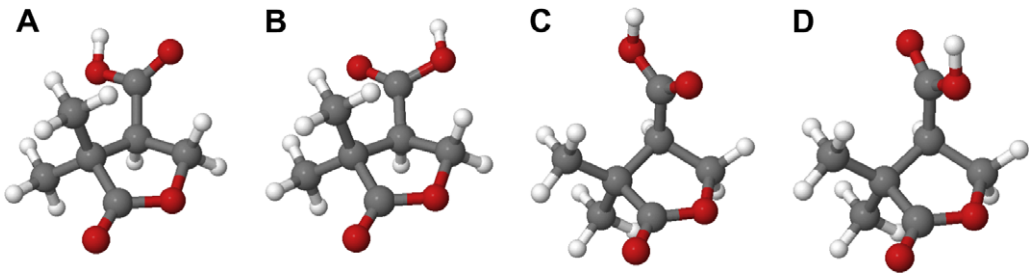


Figure 4. The four conformers of acid **1** (labelled A to D). Structures optimized in methanol.

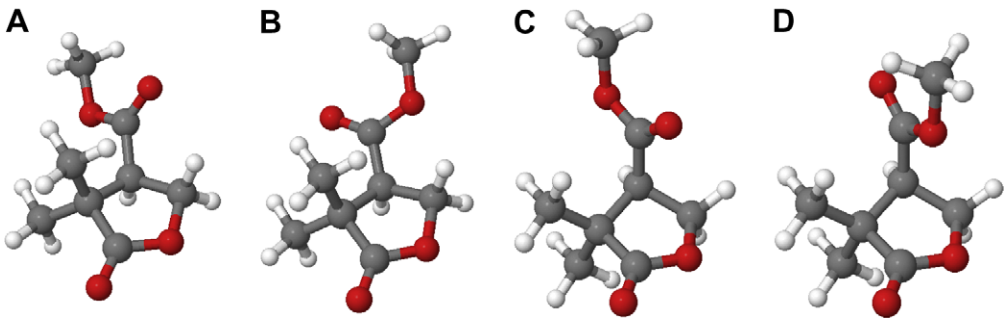


Figure 5. The four conformers of methyl ester **2** (labelled A to D). Structures optimized in methanol.

Table 4
4,4-Dimethylparaconic acid **1**

Conf.	X_i	589.3 nm		578.0 nm		546.0 nm		436.0 nm	
		$[\alpha]^i_\lambda$	$[\alpha]^{i,w}_\lambda$	$[\alpha]^i_\lambda$	$[\alpha]^{i,w}_\lambda$	$[\alpha]^i_\lambda$	$[\alpha]^{i,w}_\lambda$	$[\alpha]^i_\lambda$	$[\alpha]^{i,w}_\lambda$
In vacuo									
A	81.21	−19.113	−15.52	−20.027	−16.26	−23.037	−18.71	−41.245	−33.49
B	10.64	−38.946	−4.12	−40.692	−4.33	−46.264	−4.92	−79.195	−8.43
C	5.55	+61.373	+3.41	+64.245	+3.57	+73.628	+4.09	+131.394	+7.30
D	2.60	+91.643	+2.12	+85.451	+2.22	+97.896	+2.54	+173.593	+4.51
Total $[\alpha]_\lambda$			−14.14		−14.81		−17.0		−30.12
In methanol									
A	58.77	+16.055	+9.44	+16.866	+9.91	+19.737	+11.60	+38.044	+22.36
B	13.17	−24.543	−3.23	−25.619	−3.37	−29.676	−3.91	−49.588	−6.53
C	17.27	+81.586	+14.09	+85.254	+14.72	+96.832	+16.72	+166.931	+28.83
D	10.79	+79.939	+8.62	+83.587	+9.44	+95.675	+10.32	+166.571	+17.97
Total $[\alpha]_\lambda$			+28.92		+30.28		+40.4		+74.5
Expt. $[\alpha]_\lambda$			+12.9		+13.5		+15.5		+27.1

Specific rotation values at four different wavelengths (nm) in vacuo and in methanol: absolute $[\alpha]^i_\lambda$, weighted $[\alpha]^{i,w}_\lambda$, and total $[\alpha]_\lambda$ from the conformers optimized in vacuo and in methanol, respectively. T = 298.15 K. The AC chosen a priori in the calculations is (*R*). The experimental values were recorded in methanol at room temperature and a concentration of 0.31 g/100 mL.

Table 5
Methyl 4,4-dimethylparaconate **2**

Conf.	X_i	589.3 nm		578.0 nm		546.0 nm		436.0 nm	
		$[\alpha]^i_\lambda$	$[\alpha]^{i,w}_\lambda$	$[\alpha]^i_\lambda$	$[\alpha]^{i,w}_\lambda$	$[\alpha]^i_\lambda$	$[\alpha]^{i,w}_\lambda$	$[\alpha]^i_\lambda$	$[\alpha]^{i,w}_\lambda$
In vacuo									
A	78.39	+21.352	+16.74	+22.259	+17.45	+25.177	+19.74	+41.505	+32.53
B	12.58	−58.072	−7.31	−60.647	−7.63	−69.085	−8.69	−117.541	−14.79
C	5.80	+120.080	+6.97	+125.569	+7.29	+143.417	+8.32	+250.433	+14.53
D	3.23	+55.711	+1.80	+58.255	+1.88	+66.679	+2.16	+116.372	+3.76
Total $[\alpha]_\lambda$			+18.20		+18.99		+21.52		+36.04
In methanol									
A	59.84	+41.491	+24.83	+42.976	+25.72	+48.795	+29.20	+82.056	+49.10
B	12.01	−39.194	−4.71	−40.512	−4.86	−45.975	−5.52	−77.325	−9.28
C	19.30	+145.278	+28.05	+151.899	+29.32	+173.434	+33.48	+298.526	+57.63
D	8.85	+59.622	+5.28	+62.207	+5.51	+71.007	+6.28	+121.840	+10.78
Total $[\alpha]_\lambda$			+53.44		+55.68		+63.44		+108.23
Expt. $[\alpha]_\lambda$			+20.4		+20.8		+23.6		+39.6

Specific rotation values at four different wavelengths (nm) in vacuo and in methanol: absolute $[\alpha]^i_\lambda$, weighted $[\alpha]^{i,w}_\lambda$, and total $[\alpha]_\lambda$ from the conformers optimized in vacuo and in methanol, respectively. T = 298.15 K. The AC chosen a priori in the calculations is (*R*). The experimental values were recorded in methanol at room temperature and a concentration of 0.25 g/100 mL.

stabilization of the three other conformers, and in particular of conformer C. Turning our attention to the specific rotations, and analyzing the consequences of including the solute–solvent interaction on the conformational space and on the specific rotation results, we noted that for molecule **1**, two conformers (A and B) have negative specific rotation in vacuo but only one of them (the B conformer) has negative specific rotation in solution, see Table 4. In vacuo, the specific rotation is clearly dominated by the negative contribution from the A conformer, whereas the specific rotations of the B and C conformers cancel each other. This yields a total negative specific rotation, with values ranging from −14 to −30, depending on the wavelength of the incident light. In solution the A conformer (still the most populated one, but with lower statistical weight) reverses the sign. This is accompanied by a reduction in magnitude of the (negative) specific rotation value for the B conformer and an increase, both in magnitude and in statistical weight, of the positive specific rotation contributions of the C and D conformers, yielding a total positive specific rotation in the range of 28–75. The experimental values recorded in methanol on the synthesized enantiomer of unknown AC are in between +12 and +27. The remarkable behaviour of the computed specific rotation of conformer A does not appear to be related to basis set incompleteness, as it also occurs in sample calculations using a larger aug-cc-pVTZ basis (both in the geometry optimization step and in the property determination). It does not seem to be attributable to the specific solvent we used either, since the previously men-

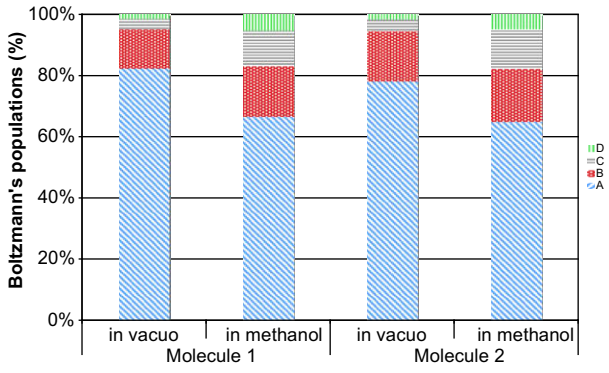


Figure 6. Percentage population fractions X_i of the various conformers (labelled A to D) in vacuo and in methanol.

tioned calculations carried out in acetonitrile yield results which are completely analogous to those obtained in methanol.

Molecule **2**, which as a consequence of the synthetic procedure adopted, has the same AC of **1**, (as also chosen a priori in the calculation) and shows population fractions similar to those of molecule **1** both in vacuo and in solution, with the C and D contributions almost canceling each other in vacuo. In contrast to molecule **1**, however, the A conformer (the most populated one) has a positive specific rotation both in vacuo and in methanol, which always results in a total positive rotatory power: 18–36 in the first case, and 53–108 in the second one. The magnitude of the specific rotation in the solvated case is larger, due to the large contribution from the C conformer to the total specific rotation. Experimental values range from +20 to +40.

Thus, whereas the in vacuo calculations predict different signs at all frequencies for the specific rotation of the acid and the methyl ester, starting from the same AC, the calculations in solution yield the same sign for both systems and at all frequencies, which is in agreement with the experimental values; see also Figures 7 and 8 for a plot of the wavelength dependence of the computed total specific rotation and of its experimental counterpart.

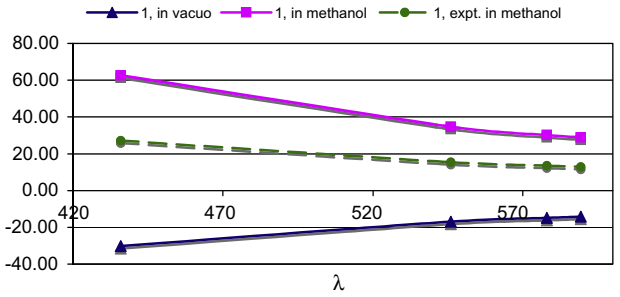


Figure 7. Dispersion of the computed and experimental specific rotations for molecule **1**. Wavelengths are expressed in nm in abscissa, specific rotations ($[\alpha]_\lambda$) are expressed in 10^{-1} deg cm^2 g^{-1} in ordinate.

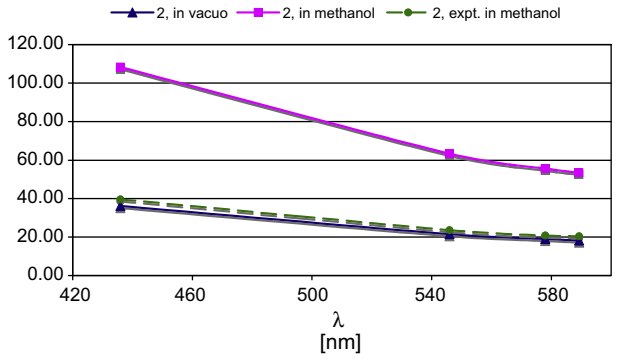


Figure 8. Dispersion of the computed and experimental specific rotations for molecule 2. Wavelengths *in abscissa* are expressed in nm, specific rotations ($[\alpha]_\lambda$) are expressed in 10^{-1} deg cm^2 g^{-1} in ordinate.

A reversal in sign between the vacuo and solvated calculations similar to the one of acid **1** has previously been observed also for the (3*S*,4*R*) enantiomer of *cis*-ethyl 4-methyl-5-oxo-tetrahydrofuran-3-carboxylate,[7] where it was concluded that the solvent effect was too significant to be neglected, and that the specific rotation results from vacuum calculations alone were not enough to allow for a reliable assignment of the AC.

In view of the fact that, on the basis of the results on the in vacuo calculations alone, we would (i) predict an AC for the acid that is the opposite to the one predicted in the solvated case, and (ii) erroneously predict that acid and methyl ester have different ACs, and supported by the experience we have gained over the years on the computational determination of the conformational space and specific rotation of paraconic derivatives,[7,26c,30] we believe that only the results of the PCM calculations can be trusted, and thus allow us assign the AC of molecules **1** and **2** (and thus also of molecule **3**) as (*R*)-(+). This assignment appears to be in agreement with the approach used in one of the previous sections based on a comparison of the experimental CD curves of similar compounds.

3. Conclusions

We have presented a synthetic procedure to obtain three new derivatives of paraconic acid, namely 4,4-dimethyl-5-oxo-tetrahydro-3-furancarboxylic acid, methyl 4,4-dimethyl-5-oxo-tetrahydro-3-furancarboxylate and ethyl 4,4-dimethyl-5-oxo-tetrahydro-3-furancarboxylate.

To determine their absolute configurations we carried out a (time dependent) DFT study of the conformational space and specific rotation of the acid and methyl ester. The systems treated are characterized by a relatively high degree of conformational flexibility and therefore constitute a challenging class of compounds from a computational point of view. Solvent effects have been included via the polarizable continuum model both during the optimization process aiming at determining all energetically relevant conformers, and in the specific rotation calculation.

For the acid we observed that the inclusion of the solvent in the molecular simulation reverses the sign of the computed specific rotation at all frequencies, as previously observed for another derivative of paraconic acid.[7] For the methyl ester, on the other hand, the sign of the total specific rotation is the same both in vacuo and in the solvated case.

From the results obtained for the two compounds, we conclude that the absolute configurations of the title compounds are (*R*)-(+).

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), using deuterochloroform as a solvent and tetramethylsilane as the internal standard. Chemical shifts are expressed in parts per million (δ). Coupling constants are given in hertz. 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). GLC 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). 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). TLC's were performed on Merck silica gel 60 F_{254} plastic sheets (eluant: light petroleum-ethyl acetate). Flash chromatography was run on silica gel for flash-chromatography (BDH). Light petroleum refers to the fraction with bp 40–70° C and ether to diethyl ether. Diethyl malonate and ethyl 2-bromo-2-methylpropionate **4** were purchased from Sigma–Aldrich.

4.2. Synthesis of substrates

4.2.1. 1,1,2-Triethyl, 2-methylpropane-1,1,2-tricarboxylate 5[36]

To a solution of 6.41 g (40 mmol) of diethyl malonate in 50 mL of anhydrous DMF, 1.60 g of 60% NaH was cautiously added at rt, under an argon atmosphere. A solution of 7.84 g (40 mmol) of ethyl

2-bromo-2-methylpropionate **4** in 5.0 mL of DMF was then added and the mixture was stirred at 70 °C for 7 days. At the end of the reaction the mixture, which is now brightly orange, was poured into a water–acetic acid solution and extracted with ether. The organic phase was washed with water and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a brown oil, which was purified by flash chromatography to afford 9.32 g (85% yield) of **5**. Amber oil; ν_{max} (neat)/cm^{-1}: 1740; ^{1}H NMR δ 4.20 (4H, q, *J* 7.1, OC*H*$_2$CH$_3$), 4.15 (2H, q, *J* 7.2, OC*H*$_2$CH$_3$), 3.91 (1H, s, H-1), 1.36 (6H, s, (C*H*$_3$)$_2$C), 1.27 (6H, t, *J* 7.1, C*H*$_3$CH$_2$O), 1.25 (3H, t, *J* 7.2, C*H*$_3$CH$_2$O); ^{13}C NMR δ 175.8 (s, *C*OOEt), 167.9 (2s, *C*OOEt), 61.3 (s, *C*(CH$_3$)$_2$), 61.1 (2t, OCH$_2$CH$_3$), 60.9 (t, OCH$_2$CH$_3$), 57.9 (d, *C*H(COOEt)$_2$), 22.9 (2q, *C*H$_3$C), 13.9 (3q, *C*H$_3$CH$_2$O); MS, *m/z*: 274 (M$^{+\cdot}$, 0.5), 229 (46), 201 (33), 184 (38), 173 (21), 160 (82), 155 (83), 129 (42), 128 (38), 127 (59), 115 (21), 101 (48), 100 (30), 99 (100), 87 (40), 83 (74).

4.2.2. Diethyl 4,4-dimethyl-5-oxo-tetrahydrofuran-3,3-dicarboxylic acid 6

To a solution of **5** (4.80 g, 17.4 mmol) in 15 mL of anhydrous ethanol, polymeric aldehyde (1.05 g, 34.8 mmol) was added, under stirring and in an argon atmosphere at rt. The mixture was heated to 80 °C and sodium ethoxide (prepared from 15 mg of sodium and 1.5 mL of anhydrous ethanol) was added. The mixture was stirred at 80 °C for 14 h. At the end of the reaction the red mixture was poured into cold water, neutralized with H_2SO_4 conc. and extracted with ether. The organic phase was washed with water and dried over anhydrous Na_2SO_4. After evaporation of the solvent **6** was obtained in 89% yield (4.00 g). Colourless oil; ν_{max} (neat)/cm^{-1}: 1803, 1730; ^{1}H NMR δ 4.51 (2H, s, H-2), 4.29 (4H, q, *J* 7.1, OC*H*$_2$CH$_3$), 1.34 (6H, s, (C*H*$_3$)$_2$C), 1.31 (6H, t, *J* 7.1, C*H*$_3$CH$_2$O); ^{13}C NMR δ 178.7 (s, C-5), 167.7 (2s, *C*OOEt), 67.8 (t, C-2), 63.1 (s, *C*(COOEt)$_2$), 62.2 (2t, OCH$_2$CH$_3$), 44.5 (s, *C*(CH$_3$)$_2$), 20.5 (2q, C(*C*H$_3$)$_2$), 13.9 (2q, *C*H$_3$CH$_2$O); MS, *m/z*: 258 (M$^{+\cdot}$, 0.8), 213 (20), 186 (12), 173 (30), 168 (14), 157 (17), 155 (28), 140 (20), 127 (35), 122 (85), 113 (60), 112 (48), 111 (40), 99 (33), 96 (22), 95 (100), 87 (21), 83 (26), 70 (24), 69 (28), 68 (24), 67 (77), 59 (52), 55 (42), 53 (22), 45 (13).

4.2.3. 4,4-Dimethyl-5-oxo-tetrahydrofuran-3-carboxylic acid 1

Lactone **6** (2.00 g, 7.7 mmol) was added to 54 mL of 20% HCl and refluxed for 52 h. After evaporation of the solvent the acid **1** was obtained (1.13 g, 93% yield). White solid, mp 130–138 °C; ν_{max} (Nujol)/cm^{-1}: 3080, 1786, 1693. ^{1}H NMR δ 4.43 (2H, AB part of an ABX system, H-2), 3.24 (1H, t, *J* 8.6, C*H*COOH), 1.45 (3H, s, C*H*$_3$C), 1.25 (3H, s, C*H*$_3$C);^{1}H NMR δ (D$_2$O) 4.39 (2H, d, *J* 7.5, H-2), 3.22 (1H, t, *J* 7.5, C*H*COOH), 1.25 (3H, s, C*H*$_3$C), 1.07 (3H, s, C*H*$_3$C); ^{13}C NMR δ (D$_2$O + acetone) 183.6 (s, C-5), 173.5 (s, COOH), 66.6 (t, C-2), 50.3 (d, *C*HCOOH), 41.7 (s, *C*(CH$_3$)$_2$), 23.1 (q, *C*H$_3$C), 18.8 (q, *C*H$_3$C); MS, *m/z*: 158 (M$^{+\cdot}$, 0.3), 114 (10), 99 (15), 83 (15), 70 (21), 69 (75), 59 (46), 56 (25), 55 (29), 53 (14), 43 (21), 42 (17), 41 (100), 39 (42).

4.2.4. Methyl 4,4-dimethyl-5-oxo-tetrahydrofuran-3-carboxylate 2

To a solution of 1.03 g (6.5 mmol) of **1** in 50 mL of anhydrous methanol, 2.5 mL (20 mmol) of trimethyl silyl chloride was added and stirred overnight under an argon atmosphere at rt. After evaporation of the solvent the corresponding methyl ester **2** was obtained in 92% yield (1.11 g) as a yellow oil. ν_{max} (neat)/cm^{-1}: 1776, 1732; ^{1}H NMR δ 4.42 (2H, AB part of an ABX system, J_{AX} 7.7, J_{BX} 9.2, J_{AB} 9.5, H-2), 3.77 (3H, s, OCH$_3$), 3.19 (1H, dd, X part of an ABX system, J_{AX} 7.7, J_{BX} 9.2, C*H*COOMe), 1.42 (3H, s, C*H*$_3$C), 1.16 (3H, s, C*H*$_3$C); ^{13}C NMR δ 180.0 (s, C-5), 170.0 (s, *C*OOMe), 65.3 (t, C-2), 52.2 (q, *C*H$_3$O), 51.1 (d, *C*HCOOMe), 41.6 (s, *C*(CH$_3$)$_2$), 24.4 (q, *C*H$_3$C), 19.8 (q, *C*H$_3$C); HRGC (γ-CDX): R_t 31.05 min for enantiomer (*S*) and R_t 31.78 min for enantiomer (*R*) (100 °C 10 min, 3 °C/min, 150 °C).

4.2.5. Ethyl 4,4-dimethyl-5-oxo-tetrahydrofuran-3-carboxylate 3

To a solution of 1.03 g (6.5 mmol) of **1** in 50 mL of anhydrous ethanol, 2.5 mL (20 mmol) of trimethyl silyl chloride was added and stirred overnight under an argon atmosphere at rt. After evaporation of the solvent the corresponding ethyl ester **3** was obtained in 93% yield (1.12 g) as a colourless oil. The latter was purified by flash chromatography (eluant: petroleum ether/ethyl acetate 85:15) giving the pure product with 79% yield. ν_{max} (neat)/cm^{-1}: 1790, 1740; ^{1}H NMR δ 4.45 (1H, t, *J* 8.7, H-2), 4.39 (1H, t, *J* 8.7, H-2), 4.24 (1H, q, *J* 7.2, OC*H*$_2$CH$_3$), 4.22 (1H, q, *J* 7.2, OC*H*$_2$CH$_3$), 3.18 (1H, t, *J* 8.7, C*H*COOEt), 1.41 (3H, s, C*H*$_3$C), 1.31 (3H, t, *J* 7.2, C*H*$_3$CH$_2$O), 1.17 (3H, s, C*H*$_3$C); ^{13}C NMR δ 179.9 (s, C-5), 169.3 (s, *C*OOEt), 65.2 (t, C-2), 61.1 (t, OCH$_2$CH$_3$), 50.8 (d, C*H*COOEt), 41.4 (s, *C*(CH$_3$)$_2$), 24.3 (q, *C*H$_3$C), 19.6 (q, *C*H$_3$C), 14.0 (q, OCH$_2$CH$_3$); MS, *m/z*: 187 (M+1$^+$, 1.2), 186 (M$^{+\cdot}$, 0.9), 142 (13), 141 (16), 114 (18), 99 (14), 96 (18), 83 (24), 70 (23), 69 (100), 68 (12), 55 (21); HRGC (γ-CDX): R_t 32.73 min for enantiomer (*S*) and R_t 33.51 min for enantiomer (*R*) (100 °C 10 min, 3 °C/min, 150 °C).

4.3. Enzymatic hydrolyses

To the lactone **3** (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 N 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 half ester 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. Ethyl (*R*)-(+)-4,4-dimethyl-5-oxo-tetrahydrofuran-3-carboxylate 3

Lactone (±)-**3** (1.15 g, 6.16 mmol) was hydrolyzed with HLAP (1.05 g) in 60 mL phosphate buffer following the general procedure. After 10 min (11% conversion) the lactone from ring fission (+)-**3** was recovered in admixture with the lactonic acid (−)-**1**. Purification by flash chromatography afforded (+)-**3** in 10% yield. $[\alpha]_D^{25} = +11.3$ (*c* 0.45, CHCl$_3$); 94% ee (determined by chiral HRGC on a γ-CDX column).

4.3.2. (*R*)-(+)-4,4-Dimethyl-5-oxo-tetrahydrofuran-3-carboxylate 1

Lactone (±)-**3** with 94% ee was hydrolyzed under acidic conditions (6 M HCl, reflux) to give the corresponding lactonic acid (+)-**1** in quantitative yield. (+)-**1**: white solid, mp 156–158 °C; $[\alpha]_D^{25} = +8.2$ (*c* 0.68, CHCl$_3$); ee 94% (determined by chiral HRGC of its methyl ester derivative on a γ-CDX column).

4.3.3. Methyl (*R*)-(+)-4,4-dimethyl-5-oxo-tetrahydrofuran-3-carboxylate 2

Lactone (+)-**1** with 94% ee was esterified with CH_2N_2 to give the corresponding methyl ester derivative (+)-**2** in quantitative yield. (+)-**2**: white solid, mp 86–88 °C; $[\alpha]_D^{25} = +16.6$ (*c* 0.32, $CHCl_3$); ee 94% (determined by chiral HRGC of its methyl ester derivative on a γ-CDX column).

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