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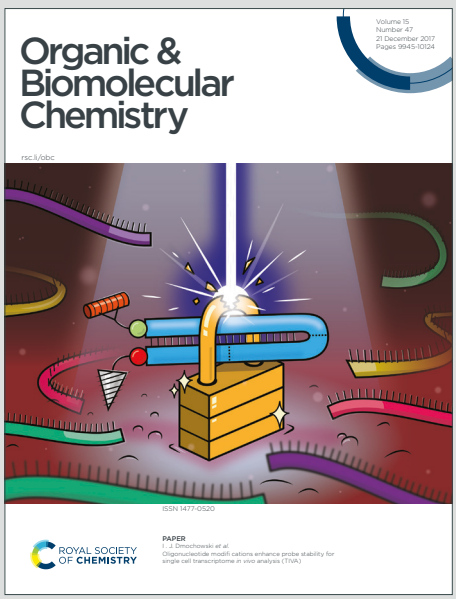

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ARTICLE

Access to valuable building blocks by regio-and enantioselective ring-opening of itaconic anhydride using lipase catalysis.

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Herein, we report for the first time, the high regio- and enantioselective ring opening of a biobased itaconic anhydride catalyzed by the *Pseudomonas cepacia lipase* (*PCL*) in *tert*-butylmethylether (TBME) at room temperature. This approach is easy, efficient, eco-friendly and afforded in one-step a series of a highly valuable monoesters itaconates (achiral or enantioenriched) using various alcohols as nucleophiles with 100% atom economy. In all cases the β-monoester isomer was the predominant product of the reaction. Using achiral primary alcohols as substrates, a variety of novel itaconates were obtained in moderate to excellent yields (50 - 90%). For select examples, product characterization was carried out using X-ray diffraction, in addition to standard techniques. The application of this approach was performed for the preparation of enantioenriched 4-monoester itaconates via enzymatic kinetic resolution.

Introduction

The development of novel sustainable routes to accede easily to high valuable functionalized building blocks is of great pre-occupation to contemporary chemistry. [1] The exploitation of low cost bio-based molecules, as renewable starting materials, constitutes a support to the achievement of green innovation.[2] In this context, Itaconic acid (IA) as a bio-based chemical with great potential for the chemical market has been reported to be one of the 12 value-added chemicals from biomass by the US Department of Energy.[3] Their world market is about 80,000 tons per year[4] and could reach about 170,000 tons per year in 2025 with sales around US $255 million because of an increasing demand for bio-based chemicals.[5]

Itaconic acid (IA) and itaconic anhydride (IAn) are regarded as key platform molecules for the future bio-based chemical economy, this molecule can be considered fully bio-derivable, and produces reactive polyesters possessing the vinylidene double bonds.[6]

A simple and eco-friendly route to produce the monoester itaconates quantitatively at low costs is enzymatic catalysis, lipases are natural benign catalysts, showing a specific catalysis as well as recyclable character and fits very well with the principles of green chemistry and sustainability.[7]

The promising potential of itaconate-derived compounds as therapeutic agents is reflected by intense ongoing research activities.[8] Several cell-permeable derivatives of itaconate, such as dimethyl itaconate (DI), 4-octyl itaconate (4-OI) and ethyl itaconate (4-EI) was synthesized to imitate the action characteristics of endogenous itaconate. Those potentially therapeutic molecule candidates have generated excellent prospects in the pharmaceutical industry due to their low toxicity and high biological activity.[9] Recently, in an interesting reporting study, the 4-OI shows a potent antiviral and anti-inflammatory activity toward SARSCoV2.[10] Moreover, new organoboron biopolymers with Itaconic Anhydride have been utilized as therapeutic drugs in cancer chemotherapy.[11] Biomedical polymers from Itaconate polyesters are valuable green chemistry alternatives to petrochemical derivatives.[12] However, to the best of our knowledge, the synthesis of the monoester itaconates has is little described in the literature, either with by conventional catalysts[13] or by biocatalysts[14] and it is the itaconic acid which is used. Recently, a direct synthesis of the 4-OI from the itaconic acid using the *CALB* as biocatalysts has been reported.[15]

Among the used enzymes, lipases have been paid growing attention for their technical and environmental advantages: ease of use under mild conditions, recyclability, and biodegradability, without the use of cofactors, excellent stability in organic solvents and for their remarkable *chemo-*, *regio-* and *enantio*-selectivity.[16] Stereoselective deacylation of acylenzymes with chiral racemic secondary and even primary alcohols is largely documented and some resolutions of secondary alcohols have been reported using

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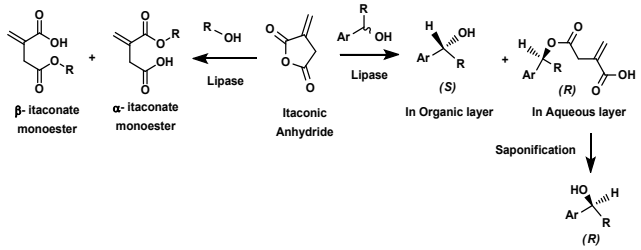
cyclic anhydrides –mainly succinic anhydride – as acylating agents.[17] This indicates that the intermediate acyl enzyme is able to discriminate between enantiomers of secondary alcohols and also, to a lesser extent, enantiomers of primary ones as well. The more frequently used enzyme is the immobilized *Candida Antarctica lipase* (CALB) for the polymerization reaction.[14a,18]

In the present work we describe, the direct synthesis of a set of alkyl, aryl and aryl-alkyl itaconate mono-esters through the regioselective ring opening of itaconic anhydride using various alcohols (primary and secondary, achiral and chiral) with an efficient biotool, the *Pseudomonas cepacia* lipase (*PCL*). The proposed approach is 100% atom economic and environmentally friendly, it was carried out at room temperature whereas the chemical route that requires high temperatures (>90°C).[19] To the best of our knowledge, the synthesis of chiral aryl-alkyl itaconate mono-esters has never been reported yet.

Results and discussion

The opening of a cyclic anhydride by an alcohol leads to an isomeric mixture of the α-monoester and the β-monoester itaconates. We know also, that the *Pseudomonas fluorescens* (Amano P) lipase catalyzes preferentially the less hindered side in ethanolysis of cyclic anhydrides substituted by alkyl at α-position in diisopropyl ether.[20] The study of the opening of the IAn was carried out with a series of achiral and chiral alcohols (primary and secondary) of different structures and with a few commercially available lipases **(Scheme 1).**

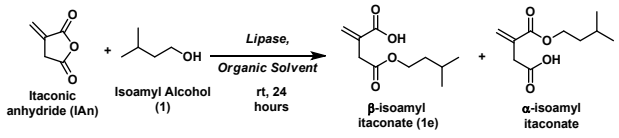


Scheme 1: Process Opening IAn with a series of primary and secondary achiral and chiral alcohols.

Optimization of reaction conditions:

Owing to the high selectivity of lipases, we have opting to explore the influence of some one's.

For the reaction model, the isoamyl alcohol **(1)** is chosen as nucleophile for the ring-opening of the itaconic anhydride (IAn). **(Scheme 2)**



Scheme 2 : Possible *regio*-isomer of mono-itaconate esters *via* enzymatic ring opening of itaconic anhydride.

To determine the appropriate reaction conditions, three commercially available lipases are selected: Lipase from *Pseudomonas cepacia* (*Amano Lipase Ps, from Burkhoderia cepacia) (PCL;* LA> 30000 U/g*), Candida rugosa* lipase (*CRL;* LA= 1170 U/mg) and the *Candida antarctica* lipase fraction B immobilized on acrylic resin (*CAL-B;* LA > 10000 U/g). All lipases are purchased from Sigma-Aldrich. The *PCL* and the *CRL* are under free form whilst the *CAL-B* is an immobilized one. The effect of the catalytic amount of biocatalysts and the solvents used are also investigated. Four solvents with various hydrophobicities are used: the TBME (logP=0.35), toluene (logP=2.52), THF (logP=0.52) and ethyl acetate (logP=0.71).

The first enzymatic reactions are carried out using an equimolar mixture of (IAn) and isoamyl alcohol in 5 mL of organic solvent. An appropriate amount of lipase is then added, and the reaction mixture is subjected to magnetic stirring at room temperature for 24 hours. The proportions of the isomeric mixture of the α-mono-isoamyl and the β-mono-isoamyl itaconates recovered after filtration of the lipase and elimination of the used organic solvent under *vaccum*, were checked by ^{1}H NMR analysis. Their quantifications were based on the chemical shifts of the double bond protons. The obtained results are summarized in Table 1.

Table 1: Regioselectivity of three lipases during the ring opening of IAn with isoamyl alcohol.

Entry [a]	*Lipase (U)*	Solvent (logP)	Itaconate monoester (β/α)[c]	Yield (%)[b]
1	Without	TBME (0.35)	-	NR
2	*CRL* (93600)		-	NR
3	*CAL-B* (1500)		40/60	60
4	*PCL* (2400)		90/10	20
5	*PCL* (3000)		90/10	27
6	*PCL* (6000)		90/10	27
7	*PCL* (9000)		90/10	60
8	*PCL* (9000)	PhMe (2.52)	90/10	5
9	*PCL* (9000)	AcOEt (0.71)	-	NR
10	*PCL* (9000)	THF (0.52)	90/10	20

[a] 1 mmol of IAn, 1 mmol of IA, in 5ml of solvent, 24h at rt. [b] Chemical isolated yield after re-crystallization in Hexane/chloroform (98 :2 v :v). [c] Regioselectivity quantified by ^{1}H NMR. NR: No reaction.

As well mentioned on Table 1, in TBME as solvent, no reaction took place in the absence of lipases, nor in the presence of *CRL* as biocatalyst (entries 1-2). Only the *CAL-B* and the *PCL* catalyze the opening of (IAn) with isoamyl alcohol **(1)**, but with opposite regioselectivities.

With the *CAL-B*, the itaconate monoester isomer **(α-1e**) is formed at a 60% proportion (entry 3). While using the *PCL*, this isomer proportion did not exceed the range of 10% and the itaconate monoester **(1e)** was recovered with an overall yield of 20% (entry 4).

As shown on figure 1, the chemical shifts at 6.46 and 5.83 ppm correspond to the double bond protons of the β-isomer form, and

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those at 6.36 and 5.74 ppm concern the double bond protons of the α-isomer form. (**Figure 1**)

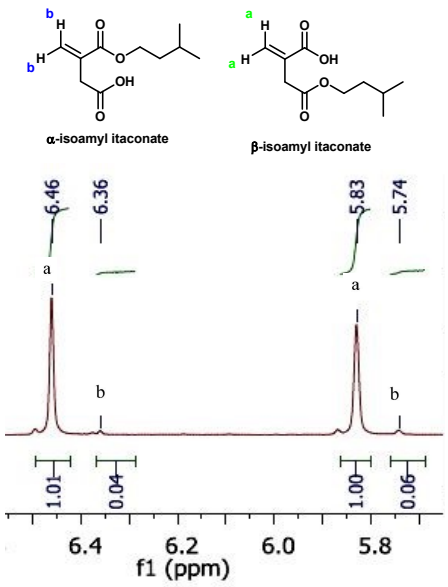


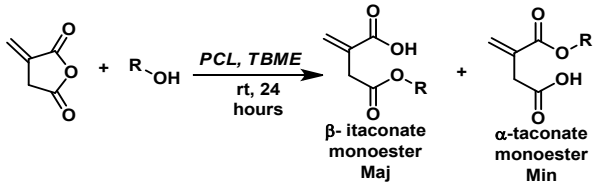
Figure 1: Zoom of ^{1}H NMR ($CDCl_3$) spectrum of isomeric mixture mono-isoamyl itaconates **1e (Table 1, entry7)**.

An improvement of the isolated chemical yield of the isomeric mixture mono-isoamyl itaconates **(1e)** from 20% to 60% was noted when increasing the amount of the *PCL* from 2400 U to 9000 U per 1mmol of IAn, and that, without affecting the lipase regioselectivity (entries 4-7), the major formed isomer is the (β-1e). A drastic decrease in the *PCL*-reactivity was recorded in the other solvents, without perturbation of the *PCL*-regioselectivity (entries 8-10). With the main objective of preparing a set of 4-monoester itaconates using our new approach, we implemented the best reaction conditions: for 1 mmol of (IAn), 9000 U of *PCL* in 5 mL of TBME.

***PCL*-catalyzed regioselective opening ring of (IAn) using a set of primary alcohols as nucleophiles:**

In order to enlighten on the regioselectivity and efficiency of the *PCL*, we applied the optimum reaction conditions and checked the impact of the various alcohols structures on the outcome of the ring-opening of (IAn) to affording the 4-monoester itaconates **(Scheme 3).**

Thus, fifteen primary alcohols of various skeletons and with a great added value were used. From the alkyl skeleton: Ethanol **(2)**, 2-Methylpropan-1-ol **(3)**, Hexan-1-ol **(4)**, Heptan-1-ol **(5)**, Decan-1-ol **(6)**, *(E)*-3,7-Dimethylocta-2,6-dien-1-ol (Geraniol) **(7)**, *(Z)*-3,7-Dimethylocta-2,6-dien-1-ol (Nerol) **(8)**. From the Arylalkanol skeleton: Phenylmethanol **(9)**, 2-Phenylethanol **(10)**, 3-Phenylpropan-1-ol **(11)**, *(E)*-3-phenylprop-2-en-1-ol **(12)**, [1,1'-biphenyl]-4-ylmethanol **(13)**. An heteroaromatic alcohol: Furan-2-ylmethanol (Furfuryl alcohol) **(14)** and a cyclic one: 2-(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethanol (Nopol) **(15)**.



Scheme 3 : *PCL*-catalyzed regioselective ring-opening of IAn using several primary alcohols as nucleophile.

The isomeric mixture of the (α / β) monoesters itaconates were recovered after filtration of the lipase and elimination of organic solvent under *vaccum*. The regioisomers ratios were checked by ^{1}H NMR analysis. Their quantifications were based on the chemical shifts of the double bond protons. The obtained results are summarized in Table 2.

As presented in Table 2, the opening ring of (IAn) catalyzed by *PCL* was promoted with high regioselectivities in favor of the β-monoester isomer with proportions range of 90%-99%, with all the alcohols used except in the case the Nopol **(15)**, bi-cyclic structure, where no reaction was shown, probably for steric constraints (entry 19). The alcohol structure intervenes significantly on the reactivity, interpreted by the isolated chemical yield of the opening-ring product.

Using *n*-alkanols as nucleophiles, an important impact of the length of the alkyl chains on both regioselectivity and reactivity is noted. The resulting monoesters itaconates **(1e-6e)** recovered with chemical isolated yield from 30% to 90% in favor of the isomer β in typically range from 90% to up to 99% (entries 1, 3, 5, 6, 8 and 9). The *PCL*-regioselectivity achieves the optimum (>99%) in favor of the β- isomer using Decan-1-ol **(6)**, the 4-Decyl itaconate **(6e)** was recovered with 90% of isolated chemical yield (entry 9). For the smaller alcohols (C:2-C:6), doubling their employed amount, a great enhancement of the *PCL*-reactivity was recorded, without any perturbation of its regioselectivity (entries 2, 4 and 7 v*ersus* 1, 3 and 6). Furthermore, we are pleased by the results obtained by two monoterpene isomers: Geraniol **(7)** and Nerol **(8)** used as nucleophiles. A high novel functionalized monoesters itaconates **(7e-8e)** are recovered with 80% of chemical yields (entries 10-11).

For the aryalkanols, those nucleophiles are used for the first time for the ring-opening of the (IAn). The obtained results match very well with the alkanols in term of regioselectivity and reactivity.

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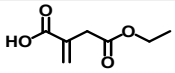
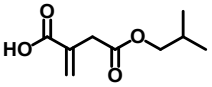
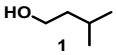
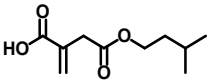
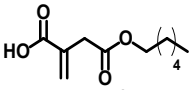
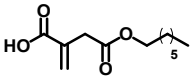
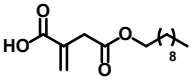
Table 2: *PCL*-catalyzed regioselective ring-opening of IAn using several primary alcohols as nucleophile

Entry	ROH	Itaconate monoester product	Yield (%) [c]	β/α (%) [d]
1 [a]			50	90/10
2 [b]	2	2e	90	
3 [a]			43	
4 [b]	3	3e	90	90/10
5 [a]			60	90/10
	1	1e		
6 [a]			30	
7 [b]	4	4e	85	90/10
8 [a]			80	97/3
	5	5e		
9 [a]			90	>99
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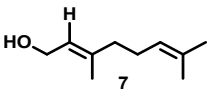
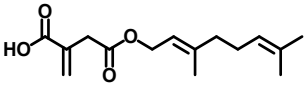
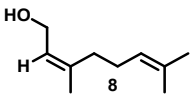
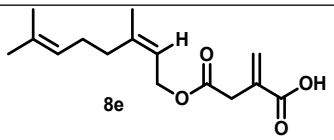
10 [a]			82	90/10
	7	7e		
11 [a]			80	90/10
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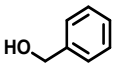
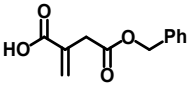
12 [a]			80	90/10
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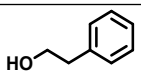
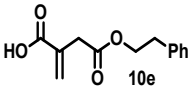
13 [a]			71	98/2
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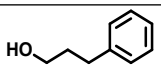
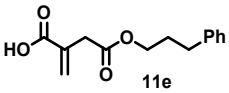
14 [a]			90	97/3
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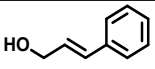
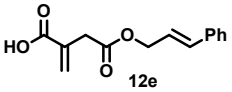
15 [a]			60	96/4
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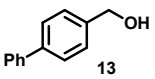
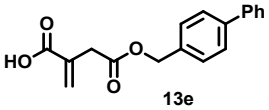
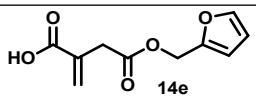
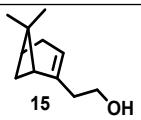
16 [a]			50	90/10
17 [b]	13	13e	50	
18 [a]			85	>99
	14	14e		
19 [a]		-	NR	-
	15			

[a] 1 mmol of IAn, 1 mmol of alcohol, 9000 U of *PCL* in 5ml of TBME, 24 hours at room temperature. [b] 2 equivalents of alcohol. [c] Isolated chemical yields evaluated after re-crystallization (hexane/chloroforme: 98 :2). [d] ^{1}H NMR quantification. NR: No reaction.

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A proportional improvement of the regioselectivity in detriment of the α-isomer with the remoteness of the hydroxyl- functions from the aromatic ring, from 10% with Phenylmethanol **(9)** to 3% with 3-Phenylpropan-1-ol **(11)** (entry 12 *versus* 14). On the other hand, using the *(E)*-3-phenylprop-2-en-1-ol **(12)** as nucleophile, a chute of the yield monoester itaconate **(12e)** was observed (60% yield) (entry 15). This fact is probably due to the mesomeric constraint of the aromatic ring conjugated allylic alcohol structure.

The moiety aryl of the nucleophile has also an impact on the reactivity of the *PCL*, where the use of Phenylmethanol **(9)** provides the product of the (IAn) ring opening with better yield (80%) then when the [1,1'-biphenyl]-4-ylmethanol **(13)** was used (50%) (entry 12 *versus* 16). No influence was recorded even by increasing the amount of the last one (entry 16 *versus* 17).

Under our optimized conditions, the ring opening of (IAn) with the furfuryl alcohol **(14)** successfully produced the monoester itaconate owing to the high regioselectivity of the *PCL* **(14e)** in favor of the β-isomer (>99%) with 85% yield (entry 18). It is important to underline that no other products are detected. This result reveals that the presence of the *PCL* lipase promotes the esterification and prevents the Diels-Alder cyclo-addition reaction of the furfuryl alcohol and itaconic anhydride. We were pleased to obtain a set of novel 4-monoester itaconates **(1e-14e)** in single step by regioselective opening of itaconic anhydride using a set of primary alcohols as nucleophiles. This biocatalytic transformation is a practical, 100% atom economic and environmentally friendly reaction. From the fourteen synthesized 4-monoesters itaconates, three are characterized by single-crystal X-ray analysis ,the 4-ethoxy-2-methylene-4-oxobutanoic acid **(2e)**, the 4-(decyloxy)-2-methylene-4-oxobutanoic acid **(6e)** and the 4-(benzyloxy)-2-methylene-4-oxobutanoic acid **(9e)**. Their crystal data collection and refinement parameters are given in Table 3. Their ORTEPs drawing are shown in Figure 2 .

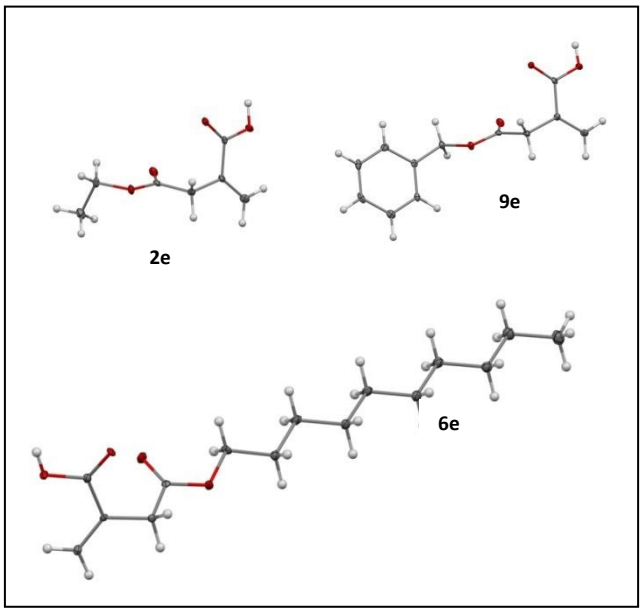


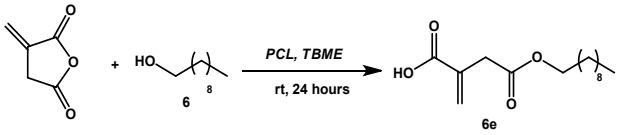
Figure 2 : An ORTEP drawing *of* compound of compounds **2e**, **6e** and **9e.** Thermal ellipsoids are shown at the 30% level.

Table 3: Crystallographic data and structure refinement details for monoesters itaconates: **2e**, **6e** and **9e**.

Compound	6e (mo_v463)	2e (mo_v468)	9e (mo_v471)
CCDC	2088740	2088738	2088739
Empirical Formula	$C_{15}H_{26}O_4$	$C_7H_{10}O_4$	$C_{12}H_{12}O_4$
M_r	270.36	158.15	220.22
Crystal size, mm^3	0.02 x 0.03 x 0.13	0.02 x 0.09 x 0.12	0.02 x 0.03 x 0.12
Crystal system	triclinic	triclinic	monoclinic
Space group	*P* -1	*P* -1	*C* 2/*c*
a, Å	5.3029(14)	5.2698(10)	17.407(9)
b, Å	5.4415(15)	7.5782(14)	5.143(2)
c, Å	28.824(8)	10.1856(19)	25.561(11)
α, °	87.791(9)	100.249(11)	90
β, °	87.437(9)	91.298(12)	110.287(13)
γ, °	66.595(8)	98.547(11)	90
Cell volume, $Å^3$	762.3(4)	395.33(13)	2146.6(17)
Z ; Z'	2 ; 1	2 ; 1	8 ; 1
T, K	100 (1)	100 (1)	100 (1)
Radiation type ; wavelength Å	MoKα ; 0.71073	MoKα ; 0.71073	MoKα ; 0.71073
F_{000}	296	168	928
μ, mm^{-1}	0.084	0.110	0.103
range, °	2.830 - 30.538	2.034 - 30.594	2.484 - 30.623
Reflection collected	24 402	16 345	38 761
Reflections unique	4 654	2 434	2 959
R_{int}	0.3134	0.3871	0.2440
GOF	0.952	0.956	1.018
Refl. obs. ($I>2(I)$)	1 863	983	1 513
Parameters	173	103	147
wR_2 (all data)	0.1471	0.1658	0.1157
R value ($I>2(I)$)	0.0945	0.0878	0.0772
Largest diff. peak and hole (e-.$Å^{-3}$)	0.308 ; -0.289	0.282 ; -0.353	0.259 ; -0.284

To demonstrate the usefulness of the optimized conditions of the ring opening of (IAn), we have envisaged checking the reusability of the biocatalyst. For that, we have chosen the Decan-1-ol **(6)** as

nucleophile, and that thanks to the good yielded product **(6e)** (90%) and the high regioselectivity (>99%). After each experiment, the *PCL* was filtered, washed with *n*-hexane, dried at 30°C and engaged directly in the next experiment **(Scheme 4)**.



Scheme 4: *PCL*-catalyzed synthesis of *4-(decyloxy)-2-methylene-4-oxobutanoic acid* (**6e**)

The *PCL* showed reactive and selective for six more cycle, the obtained 4-(decyloxy)-2-methylene-4-oxobutanoic acid **(6e)** with slight loss of the isolated chemical yield **(figure 3)**. So, the feasibility and the effectiveness of our approach have been proven with the possibility of the reuse of the biocatalyst.

In term of better valorization of our approach, we have decided to use chiral nucleophiles to preparing novel enantioenriched 4-monoester itaconates *via* enzymatic kinetic resolution.

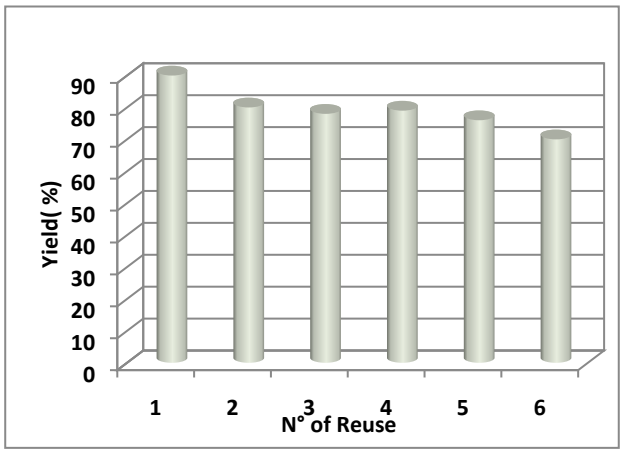
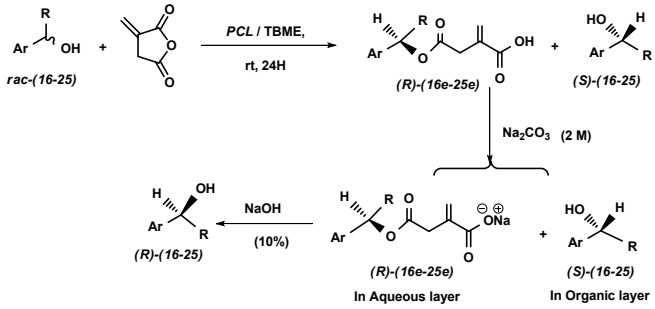


Figure 3: *PCL*-catalyzed synthesis of 4-(decyloxy)-2-methylene-4-oxobutanoic acid (**6e**): Reusability of catalyst.

***PCL*-catalyzed regioselective and enantioselective opening ring of (IAn) using a set of arylalkyl carbinols as chiral nucleophiles:**

A series of chiral arylakyl carbinols **(*rac*-16-25)** are chosen as nucleophiles for the ring-opening of the itaconic anhydride catalyzed by *PCL* to provide a new series of enantioenriched 4-monoesters itaconates. This approach, also called enzymatic kinetic resolution is the more common and practical way to preparing enantiomerically pure compounds.[21] The use of cyclic anhydride acids, as acylating agents, presents several advantages the practical one.[22] At the best of our knowledge the itaconic anhydride was never been used as acylating agent for the enzymatic kinetic resolution.

We have applied the optimal conditions defined with the primary alcohols as described on scheme 5. For each experiment, the obtained monoester itaconate and the remained alcohols were easily separated by a simple alkaline washing. The mixture of the two components was recovered by liquid–liquid extraction after dilution in ethyl acetate, the remaining (*S*)-alcohol was recovered in the organic layer and the monoester itaconate in the aqueous phase. The monoester was then extracted using ethyl acetate and then the chemical isolated yields were determined. The proportions of the isomeric mixture of the (α / β) monoesters itaconates recovered were checked by ^{1}H NMR analysis. Their quantifications were based on the chemical shifts of the double bond protons. The enantiomeric excesses of the (*R*)-monoesters itaconates are measured by chiral HPLC after saponification and obtaining the corresponding (*R*)-alcohols. The obtained results are collected in Table 4.



Scheme 5: *PCL*-catalyzed regio and enantioselective ring-opening of IAn using chiral secondary alcohols

As exposed in Table 4, the *PCL* shows moderate to good reactivities during the ring-opening of the itaconic anhydride using chiral secondary benzylic alcohols compared to the recorded results obtained with primary alcohols. The monoesters itaconates (16e-26e) are recovered at conversions varying from low to acceptable for the enzymatic kinetic resolution (EKR) reactions (4% ≤ Conv ≤ 51%). The proportions of the isomeric mixture of the (α / β) monoesters itaconates recovered were only determined for **(19e)**, **(21e)** and **(23e)**. In other cases, the isolated chemical yields were low or the quantifications based on the chemical shifts of the double bond protons were not possible. For cases where we have the opportunity to quantify the chemical shifts, we have shown that the use of the chiral secondary benzylic alcohols as nucleophiles do not disturb the high regioselectivity of the *PCL* with also the β-isomer widely predominant one between 90%->99% (entries 4, 6 & 8).

Moreover, the structure of the arylalkyl carbinol reveals a great influence on the enantioselectivity of the *PCL* during the EKR reactions using the (IAn) as acylating agent (6 ≤ E ≤ 200). The (*R*)-monoesters itaconates are obtained enantioenriched (70% ≤ ee $_P$ ≤ 98%). These influences are due to steric and electronic effects of the larger substituent of the used nucleophile, the shape of the *PCL*-active pocket and to the interactions which occur during this biotransformation.

The best regio- and enantioselectivities were recorded during the enzymatic kinetic resolution of the 1,2-dihydroacenaphthylen-1-ol **(*rac*-19)** and the 2,3-dihydro-1H-inden-1-ol **(*rac*-21)**. The (*R*)-4-((1,2-dihydroacenaphthylen-1-yl)oxy)-2-methylene-4-oxobutanoic acid **(19e)** was obtained with ee = 95% at Conv = 51% and (*R*)-4-((2,3-dihydro-1H-inden-1-yl)oxy)-2-methylene-4-oxobutanoic acid **(21e)** with ee = 98% at Conv = 45% (entries 4 & 6). Finally, it is important

to underline that no reaction was occurred using a tertiary alcohol, the linalool which was examined.

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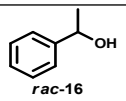
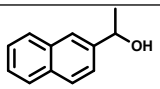
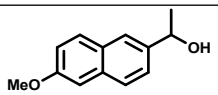
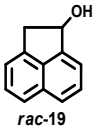
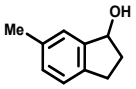
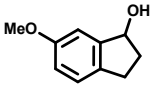
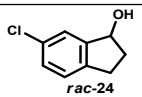
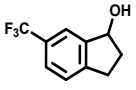
Table 4 : *PCL*-catalyzed regio and enantioselective ring-opening of chiral secondary alcohols

Entry [a]	Alcohol	ee_P (%) [b]	Yield (%) [c]	ee_S (%) [b]	Yield(%) [c]	B (%) [d]	Conv (%) [e]	E [e]
1	 *rac*-16	76	7	8	60	ND	9	8
2	 *rac*-17	94.6	6	8.6	65	ND	8	39
3	 *rac*-18	79	10	11	70	ND	12	10
4	 *rac*-19	95	40	99	45	>99	51	>200
5	 *rac*-20	72	4	3.4	53	ND	4	6
6	 *rac*-21	98	40	81	43	90	45	>200
7	 *rac*-22	75	10	12	60	ND	14	8
8	 *rac*-23	90	18	24	50	94	21	24
9	 *rac*-24	71	38	59	40	ND	45	11
10	 *rac*-25	70	36	45	52	ND	39	9

[a] 1 mmol of IAn, 1 mmol of alcohol, 9000 U of ***PCL*** in 5ml of TBME, 24 hours at room temperature.[b] Enantiomeric excess of recovered products are measured by chiral HPLC. [c] Conversion[23] : : Conv=ee_S/ee_P+ee_S ; Selectivity: E =Ln [(1-C) (1-ee_S)]/ Ln [(1-C) (1+ee_S]. [d] Isolated chemical yields evaluated after re-crystallization (hexane/chloroforme: 98 :2).[e] ^{1}H NMR quantification of the predominant isomer. ND: not determined

Conclusion

In this work, we have described, for the first time, the access to a set of achiral and enantioenriched 4-monoesters Itaconates with 100% atom economy by simple *PCL*-catalyzed ring-opening of bio-based Itaconic anhydride using various alcohols as nucleophiles. A set of novel monoesters itaconates with a high regioselectivity toward the β-isomer with a typical range of (90%->99%). The structure of the nucleophile shows an important influence on reactivity, regio- and enantioselectivity of the *PCL* lipase in this biotransformation.

Using achiral primary alcohols, fifteen examples, for the regioselective ring opening of the itaconic anhydride furnished a variety of novel potent 4-monoester itaconates **(1e-14e)** with moderate to excellent isolated chemical yields (50-90%). The structures of three of them were proved by X-ray diffraction of pure crystal: the 4-ethoxy-2-methylene-4-oxobutanoic acid **(2e)**, the 4-(decyloxy)-2-methylene-4-oxobutanoic acid **(6e)** and the 4-(benzyloxy)-2-methylene-4-oxobutanoic acid **(9e).** The sustainability of this approach was valorized by the reusability of the biodegradable biocatalyst for six cycles during the preparation 4-(decyloxy)-2-methylene-4-oxobutanoic acid **(6e)** without perturbation of the regioselectivity with slight loss of the chemical yield (90-72%).

This approach was performed for the preparation of enantioenriched 4-monoester itaconates via enzymatic kinetic resolution. The use of the itaconic anhydride as acylating agent for the enzymatic kinetic resolution of a set of arylalkyl carbinols **(*rac*-16-25)** is reported for the first time. We are pleased to obtained the potent itaconates: *(R)*-4-((1,2-dihydroacenaphthylen-1-yl)oxy)-2-methylene-4-oxobutanoic acid **(19e)** with ee = 95% at Conv = 51% and *(R)*-4-((2,3-dihydro-1H-inden-1-yl)oxy)-2-methylene-4-oxo-butanoic acid **(21e)** with ee = 98% at Conv = 45%. This work allows to considerably expanding an access to new original itaconate derivatives which are a precious resource for biological and medicinal investigations.

Experimental Section

General information

All reagents purchased from: Aldrich, were used as received. Alcohols **(1-18)** and **(20-21)** are commercially available. All used lipases are commercially available and used as purchased without any pre-treatment lipase from *Pseudomonas cepacia* (*Amano Lipase Ps, from Burkhoderia cepacia) (PCL;* Specific activity up to 30000 U/g*), Candida rugosa* lipase (*CRL;* LA= 1170 U/mg) and the *Candida antarctica* lipase fraction B immobilized on acrylic resin (*CAL-B;* LA > 10000 U/g). Reactions were monitored by thin-layer chromatography (TLC) carried out on Silica gel $60F_{254}$ plates type *MERCK* 5179, 250 *mesh*, using UV light (254 nm) the visualizing agent sing ultraviolet light (254 nm) as the visualizing agent and $KMnO_4$ solution as developing agents. The separation of the resulting alcohols and the remaining acetates was performed by liquid-liquid extraction**.**

NMR spectra were recorded on Bruker spectrometers (300 MHz for ^{1}H, 75 MHz for ^{13}C) instrument and calibrated using residual deuterated solvent as an internal reference (peak at 7.26 ppm in ^{1}H NMR and 3 peaks at 77 ppm in ^{13}C NMR in the case of $CDCl_3$ and DMSO. The following abbreviations were used to designate multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br: broad signal, dd=double-doublet. Chemical shifts were expressed in ppm and coupling constant (*J*) in Hz. The enantiomeric excesses were measured by a chiral stationary phase HPLC: *Chiralpak* OJ-H, *Chiralpak IA* or *Chiralpak IB* columns (4.6 × 250 mm). Retention times are reported in minutes. Mass spectra were taken by a MicrOTOF-Q Bruker spectrometer using electrospray ionization (ESI) analysis.

PCL*-catalyzed regioselective ring-opening of IAn using several primary alcohols*: To equimolecular mixture of itaconic anhydride and the appropriate alcohol **(1-15)** diluted in 5 mL of TBME, the adequate amount of lipase is added. After 24 hours of stirring at room temperature, the lipase was removed by filtration. The non reacted alcohol was removed by liquid-liquid extraction. The obtained monoesters recovered pure after re-crystallization in (hexane/chloroforme: 98 :2) . Complete experimental data have been provided (NMR spectra and HRMS).

4-ethoxy-2-methylene-4-oxobutanoic acid (***2e).*** White crystalline. mp 45 °C. **^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ** 9.88 (s, 1H, OH), 6.48 (s, 1H, C=C$\underline{H_2}$), 5.84 (s, 1H, C=C$\underline{H_2}$), 4.18 (q, 2H, J=7.1 Hz, C$\underline{H_2}$CH$_3$), 3.35 (s, 1H, CH$_2$-C=), 1.27 (t, 3H, *J*=7.1 Hz, CH$_2$C$\underline{H_3}$,). **^{13}C NMR (75 MHz, $CDCl_3$) δ** 171.5, 170.6, 133.3, 130.7, 61.08, 37.3, 14.1. **HRMS (ESI) m/z calcd for $C_7H_{10}O_4$ [M + Na$^+$]:**181.04**, Found:** 181.048.

4-isobutoxy-2-methylene-4-oxobutanoic acid (3e). White crystalline. mp 47 °C. **^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ** 11.2 (s, 1H, OH), 6.46 (s, 1H, C=C$\underline{H_2}$), 5.83 (s, 1H, C=C$\underline{H_2}$), 3.88 (d, 2H, *J* = 6.7 Hz, O-C$\underline{H_2}$CH), 3.35 (s, 2H, OOC-C$\underline{H_2}$-C=), 1.93 (m, 1H), 0.91 (d, 6H, *J* = 6.7 Hz, 2CH$_3$). **^{13}C NMR (75 MHz, $CDCl_3$) δ** 171.7, 170.6, 133.4, 130.6, ~~129.0~~, 71.1, ~~37.7~~, 37.3, 27.6, 18.9. **HRMS (ESI) m/z calcd for $C_9H_{14}O_4$ [M + Na$^+$]:** 209.19, **Found:** 209.0792.

4-(3- Methylbutanoxy)-2-methylene-4-oxobutanoic acid (1e). Gummy liquid · **^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ** 10 (s, 1H, OH), 6.45 (s, 1H, C=C$\underline{H_2}$), 5.82 (s, 1H, C=C$\underline{H_2}$), 4.13 (d, *J* = 6.8 Hz, 2H, O-C$\underline{H_2}$CH), 3.34 (d, 2H, *J* = 5.4 Hz, OOC-C$\underline{H_2}$-C=), 1.67 (m, 1H, CH$_2$-C$\underline{H}$(CH$_3$)$_2$), 1.51 (q, 2H, *J* = 13.5, 6.7 Hz, CH-C$\underline{H_2}$-CH$_2$,), 0.90 (d, 6H, *J* = 6.5 Hz, C$\underline{H_3}$-CH-C$\underline{H_3}$). **^{13}C NMR (75 MHz, $CDCl_3$) δ** 171.4, 170.7, 133.4, 130.5, 63.7, 37.3, 37.1, 34.04, 24.9, 22.3. 16.2, 11.11 **HRMS (ESI) m/z calcd for $C_{10}H_{16}O_4$ [M + Na$^+$]:**223.08**, Found:** 223.095.

4-(hexyloxy)-2-methylene-4-oxobutanoic acid (4e). White crystalline. mp 42 °C. **^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ** 9 (s, 1H, OH), 6.45 (s, 1H, C=C$\underline{H_2}$), 5.82 (s, 1H, C=C$\underline{H_2}$), 4.15 (t, 2H, J = 6.7 Hz, O-C$\underline{H_2}$CH$_2$), 3.34 (s, 2H, OOC-C$\underline{H_2}$-C=), 1.36 (m, 2H, O-CH$_2$-C$\underline{H_2}$-(CH$_2$)$_3$-CH$_3$), 1.28 (m, 6H, CH$_2$-(C$\underline{H_2}$)$_3$-CH$_3$), 0.90 (m, 3H, CH$_2$C$\underline{H_3}$). **^{13}C NMR (75 MHz, $CDCl_3$) δ** 171.4, 170.7, 133.4, 130.5, 65.2, 37.3, 31.3, 28.4, 25.4, 22.4, 13.9. **HRMS (ESI) m/z calcd for $C_{11}H_{18}O_4$ [M + Na$^+$]:**237.100**, Found:** 237.1102.

4-(heptyloxy)-2-methylene-4-oxobutanoic acid (5e). White crystalline. mp 53 °C. **^{1}H NMR (300 MHz, $CDCl_3$, 25°C) δ** 8.3 (s, 1H, OH), 6.47 (s, 1H, C=C$\underline{H_2}$), 5.84 (s, 1H, C=C$\underline{H_2}$), 4.11 (t, 2H, *J* = 6.7 Hz, O-C$\underline{H_2}$CH$_2$), 3.35 (s, 2H, CH$_2$-C=), 1.6 (m, 2H,C$\underline{H_2}$-CH$_2$-O), 1.30 (m, 8H, O-CH$_2$-(C$\underline{H_2}$)$_4$-CH$_3$), 0.89 (t, 3H, *J* = 9.2 Hz, CH$_2$C$\underline{H_3}$). **^{13}C NMR (75 MHz, $CDCl_3$) δ** 171.5, 170.6, 133.3, 130.6, 65.2, 37.3, 31.7, 28.8, 28.5, 25.7, 22.5, 14.07. **HRMS (ESI) m/z calcd for $C_{12}H_{20}O_4$ [M + Na$^+$]:**251.120**, Found:** 251.259.

4-(decyloxy)-2-methylene-4-oxobutanoic acid (6e) .White crystalline. mp 67 °C. **^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ** 6.48 (s, 1H, C=C$\underline{H_2}$), 5.84 (s, 1H, C=C$\underline{H_2}$), 4.12 (t, 2H, *J* = 6.7 Hz, O-C$\underline{H_2}$CH$_2$), 3.35 (s, 2H, OOCC$\underline{H_2}$-C=), 1.6 (m, 2H, C$\underline{H_2}$-CH$_2$-O), 1.30 (m, 14H, OCH$_2$-CH$_2$-(C$\underline{H_2}$)-CH$_3$), 0.8 (t, 3H, *J* = 6.7 Hz, CH$_2$C$\underline{H_3}$). **^{13}C NMR (75 MHz, $CDCl_3$) δ** 171.3, 170.6, 133.3, 130.5, 65.2, 37.3, 31.8, 29.5, 29.4, 29.29, 29.21, 28.5, 25.8, 22.6, 14.09. **HRMS (ESI) m/z calcd for $C_{15}H_{26}O_4$ [M + Na$^+$]:** 293.16**, Found:** 293.1730.

(E)-4-((3,7-dimethylocta-2,6-dien-1-yl)oxy)-2-methylene-4-oxo-butanoic acid (Mono 4-geranyl Itaconate) (7e). Gummy liquid.

^{1}HNMR (300 MHz, $CDCl_3$, 25 °C) δ 9.2 (s, 1H, OH), 6.48 (s, 1H, C=C$\underline{H}_2$), 5.84 (s, 1H, C=C$\underline{H}_2$), 5.35 (m, 1H, CH=C$^2\underline{H}$-CH$_2$), 5.33 (m, 1H, C=C$^6\underline{H}$-CH$_2$), 4.64 (d, 2H, *J* = 7.1 Hz, O-C$^1\underline{H}_2$CH), 3.35 (s, 2H, C$\underline{H}_2$-C=), 2(m, 4H,C$^4\underline{H}_2$-C$^5\underline{H}_2$), 1.7 (s, 6H,C^{9}H$_3$, C^{10}H$_3$),1.61 (s, 3H, =CC$^8\underline{H}_3$). **^{13}C NMR (75 MHz, $CDCl_3$) δ** 170.7, 170.6, 142.5, 133.4, 131.8, 130.4, 123.7, 117.9, 61.9, 39.5, 37.3, 26.2, 25.6, 17.6, 16.4. **HRMS (ESI) m/z calcd for $C_{15}H_{22}O_4$ [M + Na$^+$]:** 289.13**, Found:** 289.1408.

(Z)-4-((3,7-dimethylocta-2,6-dien-1-yl)oxy)-2-methylene-4-oxo-butanoic acid (Mono 4-Néronyl Itaconate) (8e). Gummy liquid. **^{1}HNMR (300 MHz, $CDCl_3$, 25 °C) δ** 6.48 (s, 1H, C=C$\underline{H}_2$), 5.84 (s, 1H, C=C$\underline{H}_2$), 5.35 (m, 1H, CH=C$^2\underline{H}$-CH$_2$), 5.1 (m, 1H, C=C$^6\underline{H}$-CH$_2$), 4.61 (d, 2H, *J* = 7.2 Hz, O-C$^1\underline{H}_2$CH), 3.35 (s, 2H, C$\underline{H}_2$-C=), 2.11 (m, 4H, C$^4\underline{H}_2$-C$^5\underline{H}_2$), 1.78 (s, 3H, C^{10}H$_3$), 1.69 (s, 3H, =CC$^9\underline{H}_3$), 1.61 (s, H, =CC$^8\underline{H}_3$). **^{13}C NMR (75 MHz, $CDCl_3$) δ** 171.2, 170.5, 142.8, 133.3, 132.1, 130.6, 123.5, 118.9, 61.6, 37.2, 32.1, 26.6, 25.6, 23.4, 17.6. **HRMS (ESI) m/z calcd for $C_{15}H_{22}O_4$ [M + Na$^+$]:** 289.13**, Found:** 289.1408.

4-(benzyloxy)-2-methylene-4-oxobutanoic acid **(*9e).*** White crystalline. mp 80 °C. **^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ** 10.3 (s, 1H, COO$\underline{H}$), 7.37 (m, 5H, H$_{arm}$), 6.51 (s, 1H, C$\underline{H}_2$=C), 5.86 (s, 1H, C$\underline{H}_2$=C), 5.19 (s, 2H, -COO-C$\underline{H}_2$), 3.43 (s, 2H, -C$\underline{H}_2$-COO).**^{13}C NMR (75 MHz, $CDCl_3$) δ** 171.5, 170.4, 135.6, 133.2, 130.9, 128.5, 128.2, 128.1, 66.8, 37.3. **HRMS (ESI) m/z calcd for $C_{12}H_{12}O_4$ [M + Na$^+$]:** 243.05**, Found:** 243.0641.

4-(2-phenylethoxy)-2-methylene-4-oxobutanoic acid (10e). White crystalline. mp 83 °C. **^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ** 7.25 (m, 5H, H$_{arm}$), 6.48 (s, 1H, C$\underline{H}_2$=C), 5.82 (s, 1H, C$\underline{H}_2$=C), 4.34 (t, 2H, *J* = 7 Hz, COO-C$\underline{H}_2$-CH$_2$-Ar), 3.35 (s, 2H, -C$\underline{H}_2$-COO), 2.96 (t, 2H, *J* = 7.2 Hz, -CH$_2$-Ar). **^{13}C NMR (75 MHz, $CDCl_3$) δ** 171.3, 170.2, 137.5, 133.1, 130.9, 128.9, 128.5, 126.5, 65.5, 37.2, 34.9. **HRMS (ESI) m/z calcd for $C_{13}H_{14}O_4$ [M + Na$^+$]:** 257.07**, Found:** 257.0787

4-(3-phenylethoxy)-2-methylene-4-oxobutanoic **acid (11e)**. White crystalline. mp 86 °C **^{1}HNMR (300 MHz, $CDCl_3$, 25 °C) δ** 8.6 (s, 1H, OH), 7.25 (m, 5H, H$_{arm}$), 6.49 (s, 1H, C$\underline{H}_2$=C), 5.85 (s, 1H, C$\underline{H}_2$=C), 4.15 (t, 2H, *J* = 6.5 Hz, COO-C$\underline{H}_2$-(CH$_2$)$_2$-Ar), 3.37 (s, 2H, -C$\underline{H}_2$-COO), 2.7 (m, 2H, CH$_2$-C$\underline{H}_2$-Ar), 1.98 (m, 2H, -C$\underline{H}_2$-CH$_2$-Ar). **^{13}C NMR (75 MHz, $CDCl_3$) δ** 171.4, 170.7, 141.1, 133.3, 130.7, 128.4, 126.0, 64.3, 37.3, 32.0, 30.1. **HRMS (ESI) m/z calcd for $C_{14}H_{16}O_4$ [M + Na$^+$]:** 271.08**, Found:** 271.0940.

4-(cinnamyloxy)-2-methylene-4-oxobutanoic acid (12e). White crystalline. mp 87 °C. **^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ** 7.36 (m, 5H, H$_{arm}$), 6.6 (d, 1H, *J*= 15.9 Hz, CH=C$\underline{H}$-Ph), 6.49 (s, 1H, CH$_2$=C), 6.31 (m, 1H, C$\underline{H}$=CH-Ph), 5.87 (s, 1H, C$\underline{H}_2$=C), 4.7 (dd, 2H, *J* = 6.4, 1 Hz, COO-C$\underline{H}_2$-CH=CH-Ar), 3.4 (s, 2H, -C$\underline{H}_2$-COO). **^{13}C NMR (75 MHz, $CDCl_3$) δ** 171.3, 170.4, 136.1, 134.3, 133.1, 130.9, 128.6, 128.0, 126.6, 122.8, 65.6, 37.5, 29.7. **HRMS (ESI) m/z calcd for $C_{14}H_{14}O_4$ [M + Na$^+$]:** 269.07**, Found:** 269.0781.

4-([1,1'-biphenyl]-4-ylmethoxy)-2-methylene-4-oxobutanoic acid (13e). White crystalline. mp 98 °C. **^{1}H NMR *(300 MHz, $CDCl_3$)* δ** 3.4 (s, 2H, -CH$_2$-COO); 5.21 (s, 2H, COO-CH$_2$-Ph), 5.84 (s, lH, CH$_2$=C); 6.48 (s, 1H, CH$_2$=C), 7.47-7.68 (m, 9H, H$_{arm}$). **^{13}C NMR *(75 MHz, $CDCl_3$)* δ** 170.7, 170.2, 140.8, 140.6, 139.7, 128.8, 128.7, 127.5, 127.3, 127.1, 66.5, 65.0, 37.5. **HRMS (ESI) m/z calcd for $C_{18}H_{16}O_4$ [M + Na$^+$]:** 319.08**, Found:** 319.0928.

4-(furan-2-ylmethoxy)-2-methylene-4-oxobutanoic acid (14e). White crystalline. mp 75 °C. **^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ** 10 (s, 1H, OH), 7.43 (, 1H, CH=C$\underline{H}$-O), 6.49 (s, 1H, CH$_2$=C), 6.42 (m, 1H, C$\underline{H}$=CH), 6.37 (m, 1H, C$\underline{H}$=CH) 5.85(s, 1H, CH$_2$=C), 5.12(s, 2H, COO-C$\underline{H}_2$-CH=), 3.38 (s, 2H, -C$\underline{H}_2$-COO). **^{13}C NMR (75 MHz, $CDCl_3$) δ** 171.4, 170.3, 149.1, 143.3, 133.03, 131.07, 110.8, 110.5, 58.7, 37.1. **HRMS (ESI) m/z calcd for $C_{10}H_{10}O_5$ [M + Na$^+$]:**233.03**, Found:** 233.0421.

Crystallographic data and structure refinement details for monoesters itaconates: 2e, 6e and 9e . X-ray diffraction data for compounds (**6e**: **mo_v463), (2e: mo_v468)** & **(9e: mo_v471)**were collected by using a VENTURE PHOTON100 CMOS Bruker diffractometer with Micro-focus IuS source Mo Kα radiation (λ = 0.71073 Å). Crystals were mounted on a CryoLoop (Hampton Research) with Paratone-N (Hampton Research) as cryoprotectant and then flashfrozen in a nitrogen-gas stream at 100 K. For compounds, the temperature of the crystal was maintained at the selected value by means of a N-Helix Cryostream cooling device to within an accuracy of ±1K. The data were corrected for Lorentz polarization, and absorption effects. The structures were solved by direct methods using SHELXS-97[24] and refined against F^2 by full-matrix least-squares techniques using SHELXL-2018[25] with anisotropic displacement parameters for all non-hydrogen atoms. Hydrogen atoms were located on a difference Fourier map and introduced into the calculations as a riding model with isotropic thermal parameters. All calculations were performed by using the Crystal Structure crystallographic software package WINGX[26]. CCDC 2088738-2088740 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

***PCL*-catalyzed regioselective and enantioselective opening ring of (IAn) using a set of arylalkyl carbinols as chiral nucleophiles:** To equimolar mixture of itaconic anhydride and the appropriate alcohol **(*rac*-16-25)** diluted in 5 mL of TBME, the adequate amount of lipase is added. After 24 hours of stirring at room temperature, the lipase was removed by filtration. The obtained monoester itaconate and the remaining alcohols were easily separated with a simple alkaline washing. The mixture of the two components were recovered by liquid–liquid extraction after dilution in ethyl acetate, the remaining (*S*)-alcohol was recovered in the organic layer and the monoester itaconate in the aqueous phase. The monoester was then extracted using ethyl acetate and then the chemical isolated yields were determined. The proportions of the isomeric mixture of the (α / β) mono esters itaconates recovered were checked by ^{1}H NMR analysis. Their quantifications were based on the chemical shifts of the double bond protons. The enantiomeric excesses of the (*R*)-monoesters itaconates are measured by chiral HPLC after saponification and obtaining the corresponding (*R*)-alcohols.

(R)-4-((1,2-dihydroacenaphthylen-1-yl)oxy)-2-methylene-4-oxo-butanoic acid (19e). White powder. mp 140 °C. **^{1}HNMR (300 MHz, $CDCl_3$, 25 °C) δ** 09.5 (s, 1H, OH), 7.56 (m, 6H, ar), 6.67 (dd, 1H, *J* = 7.1 Hz, 2.3 Hz, CH$_2$OOCC$\underline{H}$), 6.48 (s, 1H, C=C$\underline{H}_2$*)*, 5.84 (s, 1H, C=C$\underline{H}_2$*)*, , 3.84 (dd, 1H, *J* = 18.0, 7.4 Hz *)*, 3.39 (s, 2H, , CH$_2$OOC), 3.31 (m, 1H). **^{13}C NMR (75 MHz, $CDCl_3$): δ** 171.5, 170.8, 141.6, 141.09, 137.8, 133.2, 131.1, 131.06, 128.16, 128.12, 125.5, 122.9, 121.9, 119.8, 76.4, 38.6, 37.5. **HRMS (ESI) m/z calcd for $C_{17}H_{13}O_4$ [M -1]:**281.09**, Found** 281.081.

(R)-4-((2,3-dihydro-1H-inden-1-yl)oxy)-2-methylene-4-oxobutanoic acid (21e). White powder. mp 106 °C. **^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ** 7.42 (d, *J* = 7.4 Hz, 1H, H_{arm}), 7.29 (m, 2H, H_{arm}), 6.48 (s, 1H, C=CH_2), 6.26 (dd, *J* = 7, 3.8 Hz, 1H, CHOCO), 5.85 (s, 1H, C=CH_2), 3.37 (S, 2H), 3.13 (m, 1H), 2.9 (m, 1H,), 2.52 (m, 1H), 2.13 (m, 1H). **^{13}C NMR (75 MHz, $CDCl_3$) δ** 171.1, 170.6, 144.4, 140.7, 133.3, 130.6, 129, 126.7, 125.5, 124.7, 79.07, 37.5, 32.1, 30.1. **HRMS (ESI) m/z calcd for $C_{14}H_{14}O_4$ [M -1]:**245.09**, Found** 245.816.

(R)-4-((6-methoxy-2,3-dihydro-1H-inden-1-yl)oxy)-2-methylene-4-oxobutanoic acid (23e). White powder. mp 110 °C .**^{1}HNMR (300 MHz, $CDCl_3$, 25°C) δ** 7.17 (d, *J* = 8.3 Hz, 1H, H_{arm}), 6.9 (m, 2H, H_{arm}), 6.48 (s, 1H, C=CH_2), 6.23 (dd, 1H, *J* = 7.4, 4 Hz, CHOCO), 5.85 (s, 1H, C=CH_2), 3.8 (S, 3H, , CH_3O), 3.38 (S, 2H), 3.05 (m, 1H), 2.82 (m, 1H), 2.54 (m, 1H), 2.12 (m, 1H) . **^{13}C NMR (75 MHz, $CDCl_3$) δ** 171.2, 170.5, 158.9, 142, 136.2, 130.7, 125.3, 116, 109.7, 79.1, 55.4, 37.5, 32.6, 29.3. **HRMS (ESI) m/z calcd for $C_{15}H_{16}O_5$ [M -1]:** 275.10**, Found** 275.0924.

Author Contributions

The manuscript was written through the contributions of all authors. B.N performed the experimental work and developed of the methodology, carried out formal analyses, visualized the results. M.K.M. contributed to interpreting and analysis the results. G.R. contributed to the RX analyses and their interpretations. T.M. contributed to development of the methodology and the work. L.A.Z conceived the idea, contributed implementation of the research and the analysis of the results. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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Footnote

† Electronic supplementary information (ESI) available. CCDC : 2088738-2088740. For ESI and crystallographic data in CIF or other electronic format see DOI: