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Article

Mechanoenzymology in the Kinetic Resolution of β-Blockers: Propranolol as a Case Study

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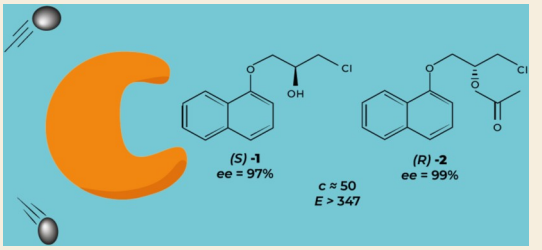
ABSTRACT: Recent advances in biotechnology, protein engineering, and enzymatic immobilization have made it possible to carry out biocatalytic transformations through alternative non-conventional activation strategies. In particular, mechanoenzymology (i.e., the use of the mechanical force produced by milling or grinding to activate a biotransformation) has become a new area in so-called "green chemistry", reshaping key fundaments of biocatalysis and leading to the exploration of enzymatic transformations under more sustainable conditions. Significantly, numerous chiral active pharmaceutical ingredients have been synthesized via mechanoenzymatic methods, boosting the use of biocatalysis in the synthesis of chiral drugs. In this regard and aiming to widen the scope of the young field of mechanoenzymology, a dual kinetic resolution of propranolol precursors was explored. The biocatalytic methodology mediated by *Candida antarctica* Lipase B (CALB) and activated by mechanical force allowed the isolation of both enantiomeric precursors of propranolol with high enantiomeric excess (up to 99% ee), complete conversion (c = 50%), and excellent enantiodifferentiation (E > 300). Moreover, the enantiomerically pure products were used to synthesize both enantiomers of the β-blocker propranolol with high enantiopurity.



KEYWORDS: *CALB, ball milling, mechanochemistry, mechanoenzymatic resolution, kinetic resolution, propranolol, active pharmaceutical ingredients, biocatalysis, β-blockers, green chemistry*

INTRODUCTION

Very recently, the search for more environmentally friendly strategies in synthetic chemistry has increased the interest in the development of green alternatives in organic, inorganic, and biological chemistry.[1,2] A wide variety of methods have been developed in order to reduce waste at the end of the chemical process while maintaining, or even increasing, the reaction yield. Among explored strategies, one can highlight the use of non-volatile solvents that can be recovered and reused and the introduction of non-conventional energy sources that help to increase the reaction efficiency.[1,2] In this regard, one of the most relevant strategies that has emerged in the past decades is the use of biocatalysts that can promote the reaction of interest with high effectiveness avoiding common difficulties observed when metallic catalysts are employed, such as the high cost associated in the production and use of those metal-containing compounds and the high risk of product contamination due to the presence of metal impurities.[1−3]

Among the most studied biocatalysts, lipases have shown high adaptability to a wide variety of reaction conditions and substrates (catalytic promiscuity);[4] moreover, recent developments in biotechnology and nanotechnology have allowed the immobilization of several lipases that can be used in the industrial production of cosmetics and biodiesel.[5−7] Moreover, enzyme immobilization enables the recovery and reuse of the biocatalyst, increasing its useful life.[5]

Significantly, synthetic properties of lipases, such as high chemo-, regio-, and enantioselectivity, which are observed using immobilized lipases under conventional heating and stirring conditions,[4,5] are retained when non-conventional sources of energy, such as sonochemistry,[8−10] microwaves,[11] or mechanical activation, are used.[12−15] Indeed, the mechanochemical activation of free and immobilized enzymes corresponds to a recently created area in mechanochemistry that has been called mechanoenzymology,[16,17] whose application in the kinetic resolution of chiral compounds has led to the synthesis of active pharmaceutical ingredients (APIs) with high enantiopurity. Mechanoenzymatic and mechanochemical methods on API's synthesis have been recently reviewed.[18−21]

Lately, our group has demonstrated the advantages of mechanoenzymatic methods in the kinetic resolution of several APIs or their precursors, by means of *Candida antarctica* Lipase B (CALB) in enantioselective acylation or enantioselective hydrolytic procedures.[13−15] Therefore, and with the aim of expanding the use of mechanoenzymology in the synthesis of

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chiral pharmaceutically important compounds, we decided to explore the mechanoenzymatic kinetic resolution of chiral β-blockers, specifically racemic propranolol precursors.

β-Blocker drugs (Figure 1) are antagonists of the β-adrenergic receptors mainly located in the heart and the

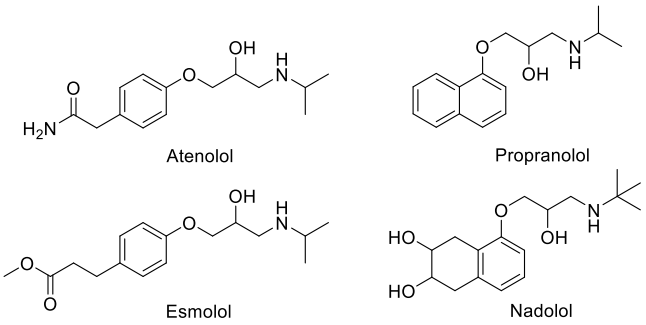


Figure 1. Selected β-blockers sold commercially as racemic mixtures.

renal juxtaglomerular apparatus; moreover, these molecules are used in the treatment of cardiovascular diseases such as high blood pressure.[22] β-Blockers are chiral molecules normally sold as a racemic mixture; however, several investigations have shown the superior activity of one of the enantiomers in the antagonism of β-receptors or the selectivity of one enantiomer for a specific adrenergic receptor.[22] A relevant illustration of the marked effect of absolute configuration on the pharmacological activity of β-blockers is the case of propranolol (Figure 2).[23] Different reports have demonstrated the higher

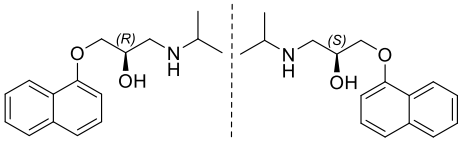


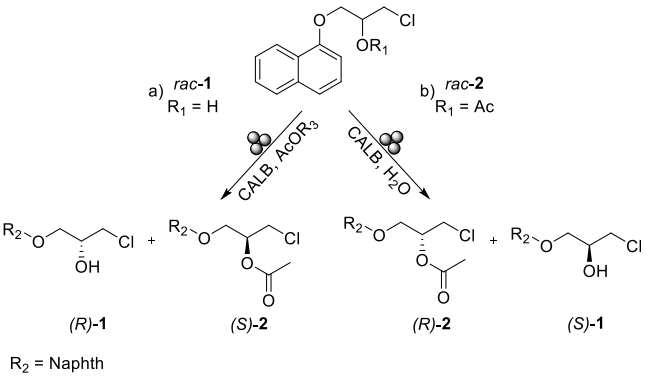
Figure 2. Mirror images of propranolol enantiomers.

antihypertensive activity of the (*S*)-enantiomer of propranolol (100 times higher) by comparison with the (*R*)-enantiomer.[23,24] Notwithstanding, (*R*)-propranolol interferes with the triyodotiroxine metabolism, leading to an alternative treatment of hyperthyroidism without the effects related to β-blocking activity.[25,26]

Numerous methodologies for the synthesis and isolation of enantiopure forms of propranolol have been developed, including the enantioselective synthesis and the kinetic resolution of relevant propranolol precursors.[27−36] However, most of the reported methodologies require the use of bulk solvents and/or expensive metallic complexes that can contaminate the final product.[27,34−38] Furthermore, biocatalytic methods have also been described with good results.[29−33]

In this context and motivated by the success achieved in our previous studies,[13−15] we decided to evaluate the potential of a mechanoenzymatic methodology using immobilized CALB (Novozym 435) and propranolol precursors in order to carry out the isolation of both enantiopure forms of this API by two different strategies: enantioselective esterification of racemic halohydrin precursors and enantioselective hydrolysis of racemic acylated precursors (Scheme 1).[39]

Scheme 1. Dual Mechanoenzymatic Kinetic Resolution via (a) Enantioselective Esterification and (b) Enantioselective Hydrolysis



RESULTS AND DISCUSSION

Propranolol precursors *rac*-**1** and *rac*-**2** were synthesized with excellent yields (85 and 92%, respectively; see the Supporting Information) following previous reports.[33]

Our first attempt on the kinetic resolution of propranolol was carried out under mechanoenzymatic conditions via enantioselective esterification of the racemic halohydrin *rac*-**1** using CALB (Scheme 1, left side). An equal amount in weight of immobilized CALB and *rac*-**1** was placed in a milling jar (stainless steel or agate with 4.6 mL capacity or Teflon with 10 mL capacity) with one ball (0.2 cm diameter for agate or stainless steel reactor or 1.0 cm for Teflon reactors. For details, see the Supporting Information), together with one equivalent of the acylating agent and 200 μL of acetonitrile (η = 1.2 μL mg^{-1}).[40,41] The resulting mixture was submitted to vibrational milling at 25 Hz for 90 min (see the Supporting Information). It is well known that the material of the milling jar and milling balls can play an important role in the outcome of the mechanoenzymatic reaction [i.e., enantioselectivity (ee), conversion (c), and enantiodifferentiation (E)].[42,43] Therefore, the influence of this variable was first investigated. Three different milling jars (agate, stainless steel, and Teflon) were evaluated in the mechanoenzymatic reaction. Similarly, good results were recorded when stainless steel or Teflon components were used ($ee_{S\text{-}2}$ = 90% and 86%, c = 9% and 9%, E = 21 and 14, respectively; Figure 3). By the same token, similar results were obtained when the biocatalytic transformation was performed using agate milling jar and milling

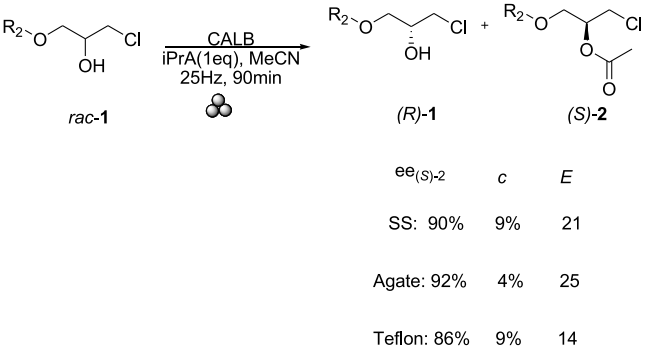


Figure 3. Results of the evaluation of the milling-jar material. SS: stainless steel milling jar. *i*PrA = isopropenyl acetate.

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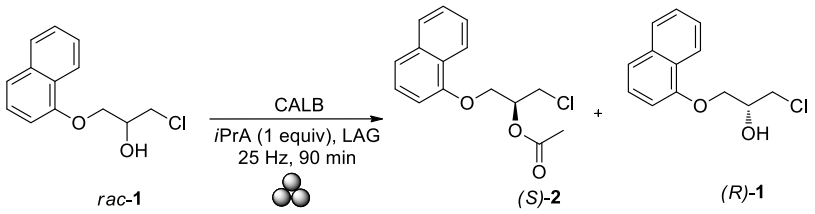
Table 1. Effect of LAG Additive in the Mechanoenzymatic Resolution of Chlorohydrin *rac*-1 via Enantioselective Acylation



entry[a]	LAG	$ee_{(S)\text{-}2}$ (%)[b]	$ee_{(R)\text{-}1}$ (%)[b]	*c* (%)[c]	*E*[d]
1	Tol	77	54	39	22
2	Diox	92	18	16	28
3	**MeCN**	**94**	**20**	**18**	**39**
4	2M2B	60	19	24	5
5	MTBE	73	26	26	8

[a]Reaction conditions: *rac*-**1** (100 mg, 0.42 mmol), CALB (100 mg), *i*PrA (1.0 equiv), LAG additive (0.2 mL), agate milling jar and balls. [b]Determined by HPLC with a chiral stationary phase. [c]Calculated from $c = ee_R/(ee_S + ee_R)$. [d]$E = \ln([1 - c(1 + ee_S)])/\ln[1 - c(1\text{-}ee_S)]$. *i*PrA: isopropenyl acetate. Tol: toluene. Diox: 1,4-dioxane. MeCN: acetonitrile. 2M2B: 2-methyl-2-butanol. MTBE: methyl *t*-butyl ether.

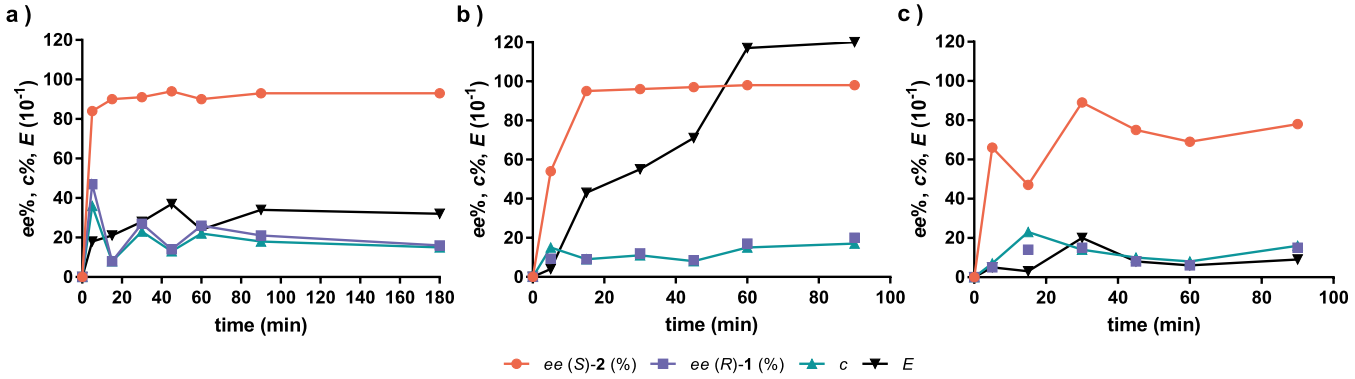


Figure 4. Enzyme kinetics for the mechanoenzymatic resolution of *rac*-**1** by enantioselective esterification. (a) Agate milling jar and balls were used. (b) Teflon milling jar and ball were used. (c) Stainless steel milling jar and ball were used.

balls ($ee_{S\text{-}2}$ = 92%, *c* = 4%, *E* = 25; see the Supporting Information).

Considering the likely presence of metal impurities generated during the milling process when metal components are employed,[12,14,44] we decided to use agate components in subsequent experiments. Several acylating agents were then examined, and the highest efficiency was found when isopropenyl acetate was used as an acylating agent in the biocatalytic process (see the Supporting Information).

Usually, the mechanochemical and mechanoenzymatic reactions are conducted under moist-solid or solventless conditions,[16] reducing solvent usage and therefore affording a less wasteful methodology. In this regard, the use of a liquid that facilitates the milling/grinding process [liquid-assisted grinding (LAG)] is crucial for driving the reaction.[40,41] Thus, the effect of a variety of LAG additives (η = 1.2 μL mg^{-1}) was evaluated in the mechanoenzymatic protocol (Table 1). It is appreciated that the polarity of the solvent used in LAG has a significant effect on the kinetic resolution process, resulting in higher product enantioselectivity as the solvent polarity increases (acetonitrile > dioxane > toluene), achieving best results when acetonitrile is used as the LAG additive (Table 1, entries 1−3). It is worthy of mention that mixed results were observed when toluene and methyl *tert*-butyl ether were tested as LAG additives (Table 1, entries 1 and 5). Indeed, the role of the LAG additive in mechanochemical reactions has not yet been fully investigated, but it has been appreciated that different LAG properties do influence the reaction outcome of CALB enzyme.[12−16,40,43]

Aiming to improve the initial results attained in the kinetic resolution of *rac*-1 (Table 1), additional reaction parameters, such as the nature and number of equivalents of the acylating agent, as well as the LAG η value, were investigated (see the Supporting Information). Nevertheless, our efforts to improve the reaction outcome were initially fruitless. Therefore, a deeper investigation of the enzyme kinetics was deemed important.

The kinetic profiles for the enzymatic resolution of *rac*-**1**-employing agate, Teflon, and stainless steel components are depicted in Figure 4. The irregular trends recorded when the kinetic resolution was carried out in agate and stainless steel components (together with rather low enantiomeric excess ee of recovered (*R*)-**1** and very low enantiodifferentiation value *E*) contrast with the gradually improving pattern that is recorded with Teflon components. In particular, the enantiopurity of the (*S*)-acetylated alcohol (*S*)-**2** and the enantiodifferentiation (*E*) value increase with time (Figure 4b).

Importantly, a homogenous distribution of immobilized catalyst and substrate seems necessary for the biotransformation to proceed with good results. In this regard, it was noticed that during the milling process using agate or Teflon milling components, the reaction mixture was stuck to the walls, evidencing inefficient mass transfer. This fact has been

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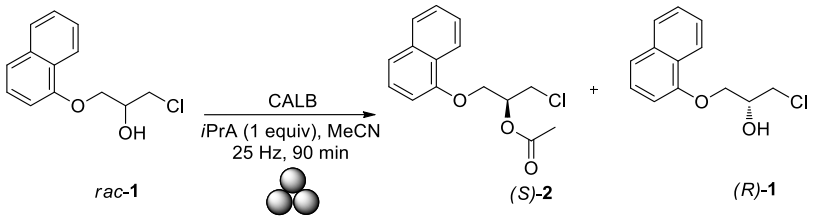
Table 2. Effect of Milling Time and Number of Milling Balls in the Mechanoenzymatic Resolution of Chlorohydrin *rac*-1 via Enantioselective Acylation



entry[a]	milling jar	milling time	number of balls	$ee_{(S)\text{-}2}$ (%)[b]	$ee_{(R)\text{-}1}$ (%)[b]	*c* (%)[c]	*E*[d]
1	agate	180	1	93	16	15	32
2	Teflon	180	1	>99	11	10	222
3	agate	90	3	>99	20	17	242
4	Teflon	90	2	>99	12	11	224
5	agate	360	3	95	19	17	47

[a]Reaction conditions: *rac*-**1** (100 mg, 0.42 mmol), CALB (100 mg), *i*PrA (1 equiv), MeCN (0.2 mL). [b]Determined by HPLC with a chiral stationary phase. [c]Calculated from $c = ee_R/(ee_S + ee_R)$. [d]$E = \ln([1 - c(1 + ee_S)])/\ln[1 - c(1\text{-}ee_S)]$. *i*PrA: isopropenyl acetate.

Scheme 2. Mechanoenzymatic Resolution of *rac*-2 via Enantioselective Hydrolysis

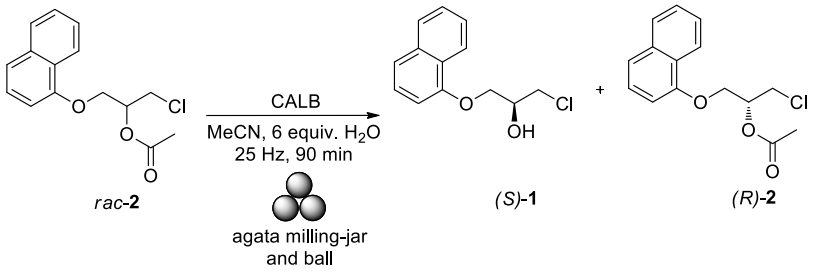
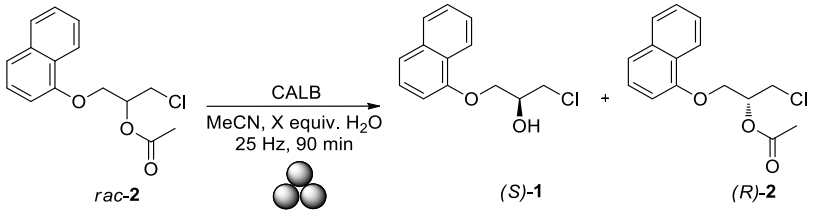


Table 3. Optimization of the Number of Water Equivalents in the Mechanoenzymatic Resolution of *rac*-2 via Enantioselective Hydrolysis



entry[a]	H_2O (equiv)	$ee_{(S)\text{-}1}$ (%)[b]	$ee(R_{)\text{-}2}$ (%)[b]	*c* (%)[c]	*E*[d]
1	0.5	95	87	48	111
2	2	98	75	43	224
3	4	98	75	43	224
4	**6**	**96**	**99**	**50**	**259**
5	8	97	62	39	124

[a]Reaction conditions: *rac*-**2** (100 mg, 0.38 mmol), CALB (100 mg), H_2O, LAG additive (0.2 mL), agate milling jar and balls. [b]Determined by HPLC with a chiral stationary phase. [c]Calculated from $c = ee_R/(ee_S + ee_R)$. [d]$E = \ln([1 - c(1 + ee_S)])/\ln[1 - c(1\text{-}ee_S)]$. MeCN: acetonitrile. 2M2B: 2-methyl-2-butanol.

previously described by our group[44] and by Bonnamour and co-workers.[45] Thus, it was deemed convenient to employ additional milling balls in the mechanochemical process to improve mixing (Table 2). The inclusion of two additional agate balls when agate components were used showed an improvement in the kinetic resolution of the racemic halohydrin relative to the use of a single ball (compare entry 3 in Table 1 with entry 3 in Table 2, affording $ee_{(S)\text{-}1}$ > 99%, $ee_{(R)\text{-}2}$ = 20%, *c* = 17, *E* = 242).

Further attempts to facilitate the mixing of the reaction mixture inside the milling jar, such as the incorporation of silica gel as a milling agent, or the use of non-conventional deep eutectic solvent in the LAG process, did not improve the reaction yield (see the Supporting Information).[44,46]

The hydrolytic kinetic resolution of *rac*-**2** was then explored using the optimized conditions encountered in the kinetic resolution of *rac*-**1**, replacing the acylating agent by water (6 equivalents) (Scheme 2).

First of all, the influence of the material of the milling jar and milling balls was examined. The enantiomeric excess in hydrolyzed (*S*)-**1** was identical when using stainless steel and Teflon components ($ee_{(S)\text{-}1}$ = 98%); nevertheless, enantiopure

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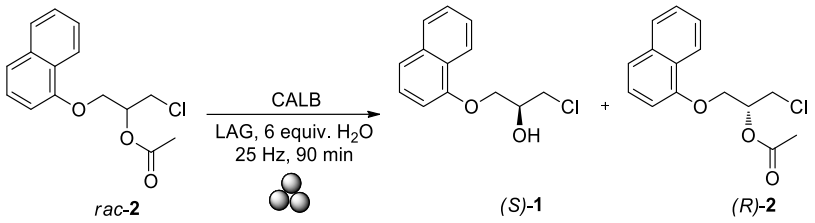
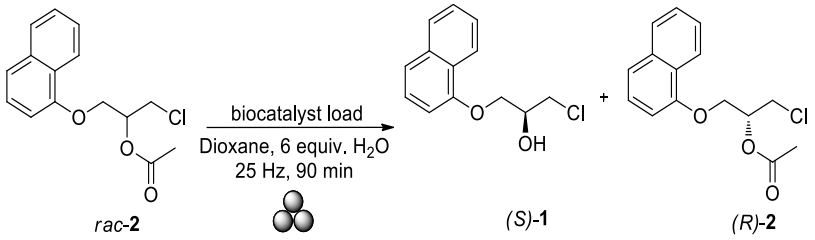
Table 4. LAG Optimization in the Mechanoenzymatic Resolution of *rac*-2 via Enantioselective Hydrolysis



entry[a]	LAG	ee(S)$_{-1}$ (%)[b]	ee(R)$_{-2}$ (%)[b]	c (%)[c]	E[d]	yield (%)
1		96	85	47	133	15
2	MeCN	96	99	50	259	50
3	n-Hex	97	76	44	151	39
4	Tol	96	75	44	110	35
5	**Diox**	**97**	**99**	**50**	**347**	**48**
6	2M2B	90	89	50	53	39

[a]Reaction conditions: *rac*-**2** (100 mg, 0.38 mmol), CALB (100 mg), H_2O, LAG additive (0.2 mL), agate milling jar and balls. [b]Determined by HPLC with a chiral stationary phase. [c]Calculated from $c = ee_R/(ee_S + ee_R)$. [d]$E = \ln([1 - c(1 + ee_S)])/\ln[1 - c(1 - ee_S)]$. Tol: toluene. Diox: dioxane. MeCN: acetonitrile. 2M2B: 2-methyl-2-butanol.

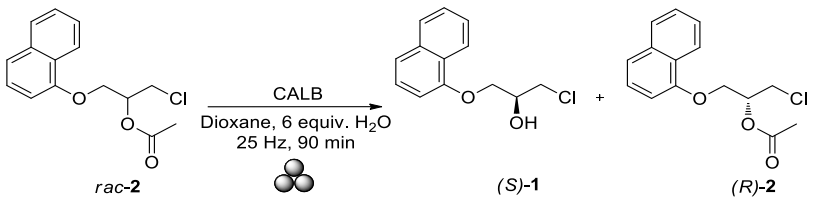
Table 5. Evaluation of the Biocatalyst Load in the Mechanoenzymatic Resolution of *rac*-2 via Enantioselective Hydrolysis



entry[a]	CALB (mg)	ee(S)$_{-1}$ (%)[b]	ee(R)$_{-2}$ (%)[b]	c (%)[c]	E[d]
1	10	79	5	6	9
2	25	98	69	41	205
3	50	94	24	20	41
4	**100**	**96**	**99**	**50**	**259**

[a]Reaction conditions: *rac*-**2** (100 mg, 0.38 mmol), CALB, H_2O (6 equiv), dioxane (0.2 mL), agate milling jar and milling balls. [b]Determined by HPLC with a chiral stationary phase. [c]Calculated from $c = ee_R/(ee_S + ee_R)$. [d]$E = \ln([1 - c(1 + ee_S)])/\ln[1 - c(1 - ee_S)]$.

Table 6. Scale-Up for the Mechanoenzymatic Resolution of *rac*-2



entry[a]	ball weight	ee(S)$_{-1}$ (%)[b]	ee(R)$_{-2}$ (%)[b]	c (%)[c]	E[d]
1	0.44	97	57	37	117
2	1.42	97	71	42	140
3	1.42[e]	96	89	49	147

[a]Reaction conditions: *rac*-**1** (1.79 mmol, 0.5 gr), CALB (100 mg), dioxane (0.2 mL), agate milling jar and milling balls. [b]Determined by HPLC with a chiral stationary phase. [c]Calculated from $c = ee_R/(ee_S + ee_R)$. [d]$E = \ln([1 - c(1 + ee_S)])/\ln[1 - c(1 - ee_S)]$. [e]12 equivalents of water were used.

(*S*)-**1** was isolated when the mechanoenzymatic process was carried out using agate components ($ee_{(S)\text{-}1}$ > 99%). Moreover, the enantiopurity of the recovered (*R*)-**2** was higher when using agate components, relative to the use of Teflon and stainless steel components ($ee_{(R)\text{-}2}$ = 99, 76, and 73%, respectively). Thus, it was decided to employ agate milling jar and milling balls in further experiments.

Relevant parameters such as the number of water equivalents (Table 3), the nature of the LAG additive (Table 4), and the enzymatic load[47] (Table 5) were optimized for the mechanoenzymatic enantioselective hydrolysis. The number of water equivalents was relevant, finding that 6 equivalents of water are the most convenient in order to improve the mechanoenzymatic strategy (Table 3, compare

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entries 1−5), achieving the formation of essentially enantiopure (*R*)-**2** [$ee_{(R)\text{-}2}$ = 99%] and highly enantioenriched (*S*)-**1** [$ee_{(S)\text{-}1}$ = 96%], with a high enantiodifferentiation *E* = 259 (Table 3, entry 4). The use of LAG additives (η = 0.83) clearly lead to improved outcome in the mechanoenzymatic resolution via enantioselective hydrolysis of *rac*-**2**, reaching excellent results when polar solvents were used (Table 4, entries 2 and 5). Best results were obtained when dioxane was used as an LAG additive (Table 4, entry 5), yielding highly enantioenriched (*S*)-**1** and essentially enantiopure recovered (*R*)-**2**.

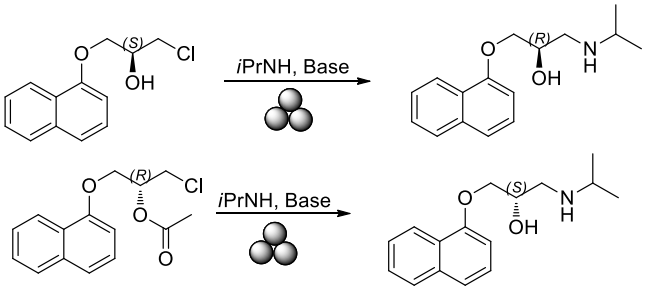
Finally, the biocatalyst load was evaluated (Table 5), finding that the optimal results for the mechanoenzymatic kinetic resolution of *rac*-**2** via enantioselective hydrolysis are obtained with dioxane as LAG, agate components, and CALB biocatalyst in a 1:1 ratio with respect to the amount of substrate (Table 5, entry 4).

One of the most challenging aspects of mechanochemical and mechanoenzymatic protocols consists in scaling-up the process. In the present study, it was decided to increase the amount of the reaction components in order to resolve half gram of substrate *rac*-**2**, using the best experimental conditions (Table 5, entry 4). A larger agate milling jar (10 mL) was employed.

Regrettably, some loss of enantiopurity of the recovered (*R*)-**2** became noticeable under the large-scale mechanoenzymatic reaction conditions (Table 6, entry 1); nevertheless, the enantiodifferentiation value was still rather good (*E* = 117). In this regard, it was found that increasing the size and weight of the agate ball (from 0.44 to 1.42 g, Table 6, entry 2) helped improve the reaction outcome.[48] Furthermore, doubling the number of equivalents of water from 6 to 12 resulted in an additional increase in the enantiodifferentiation value, reaching excellent results (Table 6, entry 3: $ee_{(S)\text{-}1}$ = 96%, $ee_{(R)\text{-}2}$ = 89%, *c* = 49%, *E* = 147).

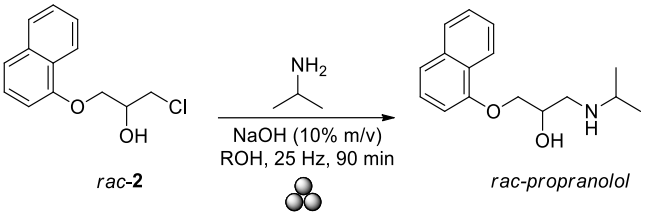
Having demonstrated the feasibility of the mechanoenzymatic method to carry out the preparation of virtually enantiopure precursors of propranolol, we envisaged a potential mechanochemical synthesis of enantiopure (*R*)-propranolol (Scheme 3). Accordingly, a series of exploratory

Scheme 3. Synthetic Strategy for the Mechanosynthesis of Both Enantiomers of Propranolol



assays, under both conventional heating and stirring conditions and under mechanochemical activation, were carried out (Table 7). In particular, the substitution of chlorine atom by the required isopropyl amino group was performed according to previously reported methods using NaOH, isopropyl amine, and isopropanol in solution, affording 83% yield of the desired product after 60 min of stirring at room temperature[49] (Table 7, entry 1).

Table 7. Synthesis of Propranolol under Conventional Heating and Stirring Conditions and under Mechanochemical Activation



rac-**2** *rac*-propranolol

entry[a]	*i*PrA (mL)	ROH (mL)	NaOH (mL)	conditions	time (min)	yield (%)[b]
1[d]	2.5	1	1	H&S	60	83
2[c]	2.5	1	1	H&S	60	50
3[d]	2.5	1	1	MCH	90	90
4[c]	2.5	1	1	MCH	90	50
5[d]	2.0	1	1	MCH	90	90
6[d]	1.5	1	1	MCH	90	88
7[d]	**1.0**	**1**	**1**	**MCH**	**90**	**87**
8[d]	0.5	1	1	MCH	90	79
9[d]	0.2	1	1	MCH	90	
10[d]	1	1	0.8	MCH	90	79
11[d]	1	1	0.6	MCH	90	73
12[d]	1	1	0.4	MCH	90	38
13[d]	1	1	0.2	MCH	90	26
14[d]	1	0.8	1	MCH	90	54
15[d]	1	0.6	1	MCH	90	72
16[d]	1	0.4	1	MCH	90	35
17[d]	1	0.2	1	MCH	90	24

[a]Reaction conditions: *rac*-**2** or (*S*)-**2** (0.42 mmol), agate milling jar and milling balls. [b]Isolated yield. [c]*i*PrOH (isopropyl alcohol) was used in this reaction. [d]*t*-BuOH (*tert*-butanol) was used in this reaction. H&S: conventional heating and stirring conditions. MCH: mechanochemical conditions.

When the substitution of chlorine by the required isopropyl amino group was carried out under mechanochemical conditions, the reaction yield increased to 90%, exhibiting higher regioselectivity (Table 7, entry 3). Nevertheless, the reaction was sensitive to the ratio of alcohol, base, and amine. With the aim of finding the best conditions to carry out this substitution reaction, it was decided to determine the best relative ratio of base, alcohol, and amine. It was found that the use of 1.0 mL of isopropylamine, 1.0 mL of *t*-butanol, and 1.0 mL of NaOH solution provided the best results (Table 7, entry 7). Finally, the optimized mechanochemical conditions for the synthesis of the β-blocker were used to synthesize both enantiomeric forms of propranolol, achieving 86% yield of the (*R*)-enantiomer and 80% yield of (*S*)-propranolol with a high enantiomeric excess.

CONCLUSIONS

β-Blockers, such as propranolol, are crucial drugs in the treatment of heart diseases. Significantly, the associated chirality of β-blockers is an essential feature for their activity, determining the biological effect of the drug and making it important for the development of methods to carry out the enantioselective synthesis of these compounds. In this regard, the mechanoenzymatic methods described in the present work highlight a green alternative in the enantioselective synthesis of enantiopure propranolol precursors, which can be easily converted into the enantiopure forms of propranolol. In

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particular, the CALB-catalyzed enantioselective hydrolysis of racemic acetylated precursors afforded both enantiomeric precursors of propranolol with high enantiomeric excess (up to 99% ee), complete conversion (c = 50%), and excellent enantiodifferentiation (E > 300). The mechanoenzymatic protocol can be scaled up to synthesize larger amounts of the enantioenriched compounds, and the final products can be used as starting materials for the synthesis of enantioenriched propranolol, again under mechanochemical activation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsorginorgau.1c00049.

Experimental part, including characterization data, copies of NMR spectra, and HPLC chromatograms (PDF)

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Author Contributions

The experimental work was carried out by G.G.-V. Both authors contributed to the planning and design of the project, and both read and approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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