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ENZYMATIC RESOLUTION OF METHYL 2-ALKYL-2-ARYLACETATES

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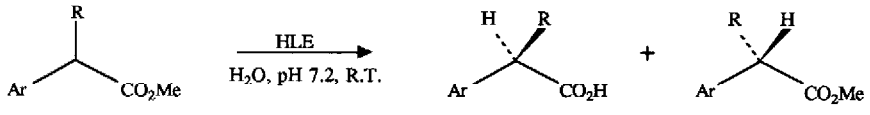
Abstract : *Horse liver esterase, used as its inexpensive commercial acetone powder, catalyzes the selective hydrolysis of methyl 2-alkyl-2-arylacetates to afford R(-)-2-alkyl-2-arylacetic acids and S(+)-methyl 2-alkyl-2-arylacetates.*

Several 2-arylpropionic acids are known as important pharmaceutical agents exhibiting non steroidal antiinflammatory activities [1] so that many chemical synthetic methods for the obtention of theses acids or their esters have been developed [1b,c]. These methods lead in general to racemic mixtures or it has been reported [1a] that the activity of these drugs are often associated with a single enantiomer : for example the S(+) enantiomers of 2-(3-phenoxyphenyl) propionic acid (Fenoprofen) or 2-(6-methoxy-2-naphtyl) propionic acid (Naproxen) are respectively 35 and 28 times more active than the corresponding R(-) enantiomers [2]. Thus, selective syntheses of the physiologically more active enantiomers are highly desirable. Different approaches have been described, including chemical resolution processes [3] or various asymmetric syntheses [4]. Recently the enantioselective enzymatic hydrolysis of different esters of 2-arylalkanoic acids catalyzed by lipases of microbial origin have been reported [5]. Most of these lipases preferentially cleaved the R-enantiomer and only the lipase from Candida cylindracea gave selectively the S- acids. The rates of conversion were generally slow and the use of activated esters was found necessary to obtain useful results [5a,d,e,f].

We report in this letter our work related to the kinetic enzymatic resolution of simple methyl esters of 2-alkyl-2-arylacetic acids 1 [6] catalyzed by horse liver esterase (HLE). This enzyme, commercially available as an inexpensive crude acetone powder, has been already used in the laboratory for the resolution of racemic lactones [7].



1 2 3

a : Ar = Ph , R = Me
b : Ar = p MeOPh , R = Me
c : Ar = m MeOPh , R = Me
d : Ar = o MeOPh , R = Me
e : Ar = p iBuPh , R = Me (Ibuprofen)
f : Ar = Ph , R = Et
g : Ar = Ph , R = iPr
h : Ar = p MeOPh , R = iPr
i : Ar = p Cl , R = iPr

The esters **1a-i** (1 mmol) in water (8 mL) were incubated with horse liver acetone powder (200 mg, Sigma) at room temperature (20°C) and pH 7.2. This pH value was maintained through the entire reaction by continuous addition of 2N NaOH aqueous solution. The reaction was stopped when either 0.4 - 0.5 equivalent or 0.5 - 0.6 equivalent of base had been consumed (obtention respectively of acids or of unreacted esters of best enantiomeric purity). The solid was removed by vacuum filtration over celite and washed with water and ether. The filtrates were extracted with ether and the organic phase was dried and concentrated to give the unreacted esters **3.** The aqueous phase was then acidified to pH 2 with 3N HCl and extracted with ether. The combined organic layers were dried and the solvent removed in vacuo to give the acids **2.**

As shown in Tables 1 and 2, the methyl esters **1a-i** were found to be excellent substrates for horse liver esterase. This enzyme selectively hydrolyzed the R enantiomers and thus allowed the obtention of R(-)-2-alkyl-2 arylacetic acids and their corresponding S(+)-methyl esters with good to high optical purity [8]. In particular, a comparison with literature data [5a,e] indicated that this crude esterase is the best catalyst for the enantioselective hydrolysis of esters of simple 2-phenylalkanoic acids such as **1a** and **1f**. Furthermore we have found that pig liver esterase (PLE), another commercial esterase, hydrolyzed very rapidly the ester **1a** but without any enantiomeric discrimination, allowing an easy obtention of the S(+)-acid from the S(+)-ester **2a**. Alternatively, the S(+)-acids could be obtained without any racemization by acid hydrolysis of the corresponding esters [4a].

Excellent enantiomeric purities were also obtained in the case of methyl 2-isopropyl-2-arylacetates **1g**, **1h** and **1i**. Thus, steric hindrance at the α position of the carbomethoxy groups greatly slowed down the hydrolysis rate, but, at the same time, improved its selectivity. These results are quite interesting since esters of 2-isopropyl-2-arylacetic acids constitute a new class of synthetic insecticides for which it has also been shown that one enantiomer is largely more active than the other [15] and since, to our knowledge, no good enzymatic resolution of these compounds has been described till now [5a].

The enantioselective hydrolysis of different others unsaturated and saturated esters catalyzed by horse liver esterase are currently under investigation.

Table 1. *HLE-catalyzed hydrolysis of methyl 2-alkyl-2 -arylacetates. Obtention of R(-)-acids* **2**

Substrate	Conv, %[a]	time,h	Produced acids 2				Recovered esters 3	
			[α], deg.[b]	lit.[α] (ref)	ee%[e]	Yield %[g]	ee%[f]	Yield %
1a	40	1.75	-63	-68(9)	92	34	43	48
1b	42	1.	-53c	-58(10)[c]	91	34	47	43
1c	45	1.75	-34		62	45	46	39
1d	41	2.5	-46	-68(11)	67	41	40	32
1e	40	11	-51	-57(12)	88	34	60	35
1f	42	2	-87[d]	-93(13)[d]	93	38	66	46
1g	48	32	-55	-60(15)	91	40	92	33
1h	46	26	-50	-53(15)	94	36	76	36
1i	46	22	-43	-47(15)	92	41	84	41

Table 2. *HLE-catalyzed hydrolysis of methyl 2-alkyl-2-arylacetates. Obtention of S(+)-esters* **3**

Substrate	Conv, % [a]	time, h	Produced acids 2		Recovered esters 3			
			ee%	yields %	[α],deg.[b]	lit.[α](ref)	ee%[f]	Yield %
1a	56	6	53	45	+107d	+109(14d)	>96	38
1b	50	4.5	72	39	+63		90	35
1c	56	4	51	38	+53		72	35
1d	55	6.75	40	39	+52		62	44
1e	58	18	66	36	+71	+70(12)	>96	31
1f	51	5	87	31	+71		>96	36
1h	52	30	91	35	+62		>96	42

a) Determined on the basis of the quantity of consumed base.
b) Unless otherwise stated the solvent is $CHCl_3$, $0.3<c<1.6$
c) In MeOH ; d) In toluene
e) Estimated but for **2c** by comparison of the values of optical rotations with known data. Confirmed for **2a, b, c, f** after esterification with diazomethane by 1H NMR spectroscopy in the presence of chiral $Eu(hfc)_3$
f) Determined by 1H NMR in the presence of chiral shift reagent = $Eu(hfc)_3$
g) Yields are given for pure isolated compounds.

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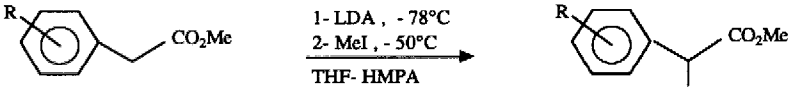
6) Esters **1a, le** and **1f-i** were obtained from commercially available corresponding acids and esters **1b, 1c, 1d** were prepared with excellent yields by alkylation :



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8) The absolute configurations of acids **2a,b,d-i** were assigned by comparison of the signs of their optical rotations with literature data. The configuration of acid **2c** was deduced by analogy, on the basis of the sign of its optical rotation.

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