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Rabbit Liver Esterase-Mediated Enantioselective Synthesis of 2-Arylpropanoic Acids

Chris H. Senanayake,* Timothy J. Bill, Robert D. Larsen, John Leazer, and Paul J. Reider

Department of Process Research, Merck Research Laboratories
Division of Merck & Co., Inc.
P.O. Box 2000, Rahway, New Jersey 07065, USA

Abstract: **A novel enzymatic resolution of ortho-substituted 2-arylpropanoic acids using rabbit liver esterase is described. The *R*-enantiomer is obtained by enzymatic hydrolysis of the ethyl ester whereas the *S*-enantiomer is obtained by enzyme mediated enantioselective transesterification of allyl propionates to their corresponding methyl esters.**

Arylpropanoic acids, such as ibuprofen and naproxen, are members of the class of non-steroidal, anti-inflammatory drugs which control the symptoms of arthritis and related connective tissue diseases.[1] Emphasis has been placed on the enantiospecific synthesis of these compounds due to their activity which is most often associated with the *S*-enantiomer.[2] One compound of this family that has not been previously prepared in optically active form is 2-(2-iodophenyl)propanoic acid; this versatile building block contains the iodo group which provides an extremely useful handle for the synthesis of medicinal agents containing an ortho-substituted chiral arylpropanoic acid moiety. In our search to prepare this intermediate in optically pure form we discovered a highly effective enzymatic resolution of ortho-substituted arylpropanoic acids with rabbit liver esterase (RLE).

After a number of approaches to prepare the optically pure arylpropanoic acid failed,[3,4] enzymatic resolution proved to be successful. The use of enzymes for the resolution of 2-arylpropanoic acids is well known.[5] Despite the previous successes of hydrolytic enzymes with this class of substrates, their ability to resolve 2-(2-iodophenyl)propanoic acid with high enantiomeric excess (e.e.) was less than desirable. In particular, traditional lipases such as *Candida cylindracea*, *Rhizopus arrhizus*, and *Pseudomonas* were unable to hydrolyze the methyl ester and pig liver esterase only provided low e.e.[6]

Rabbit liver esterase proved to have surprising selectivity for resolution of ortho-substituted arylpropanoic acids. Both enantiomers of 2-(2-iodophenyl)propanoic acid could be obtained in 85-99 % ee. The racemic acid was converted to the appropriate ester (methyl, ethyl, allyl, etc.) by treatment of the acid chloride with the corresponding alcohol in >95% yield. For resolution of the *R*-enantiomer (Scheme 1, path a), the ester was stirred in a pH 7.5 buffer (0.1 M K_2HPO_4) with Triton X-100, a non-ionic surfactant which is used to partially solubilize the ester. RLE (Sigma, E9636; 25.4 units/mmol ester) was added and the subsequently hydrolyzed (*R*)-acid was easily separated from the unhydrolyzed ester extraction with saturated aqueous $NaHCO_3$. As illustrated in Table 1, the direct hydrolysis of the ethyl ester produced the highest optical purity for the *R*-(-)-enantiomer (> 85% e.e.). Increasing the length of the ester group from ethyl to butyl did not alter the enantioselectivity. In all cases the ester portion, isolated predominantly as the *S*-(+)-enantiomer, was obtained in low e.e.(<50%).[7]

In order to increase the rate of reaction with the allyl ester and to enhance its solubility in the buffered mixture, methanol was employed as a co-solvent. This led to the serendipitous discovery of a highly effective

Scheme 1

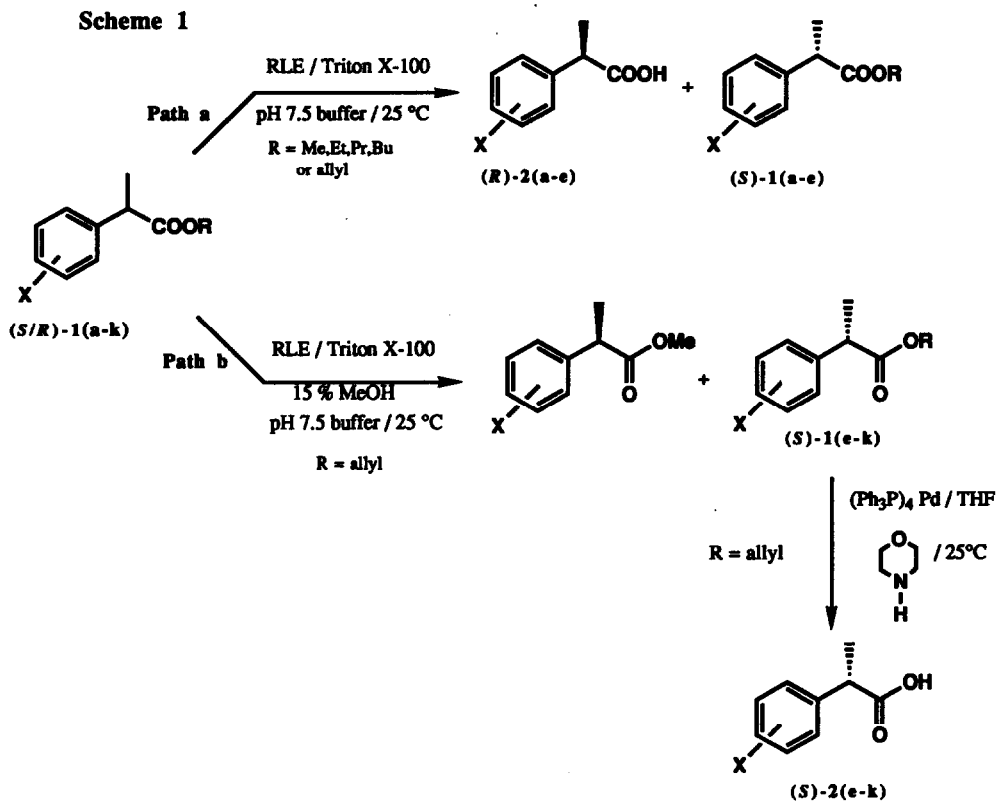

Table 1: Results of the direct hydrolysis of 2-(2-iodophenyl)propionates.

Ester (1)	R	X	time (d)	% ee of (*R*)-2[7]	% conversion to (*R*)-2
a	Me	2-I	1.6	68	47
b	Et	2-I	2.0	85	48
c	Pr	2-I	2.0	81	47
d	Bu	2-I	3.5	85	42
e	Allyl	2-I	5.0	59	42

resolution of the (*S*)-enantiomer by transesterification. In this case the selectivity of the enzyme for ester cleavage of the (*R*)-enantiomer served to leave the (*S*)-allyl ester largely unreacted. The novel RLE-mediated transesterification produced the corresponding (*R*)-methyl ester within a reasonable time period (Scheme 1, path b). Although, enzymatic transesterification reactions have been reported,[8] to the best of our knowledge this is the first instance where an allyl ester is transesterified to the methyl ester leaving the remaining allyl ester in high

The concentration of methanol was critical: A solution of <10% methanol produced a high degree of unselective hydrolysis, whereas a solution of >20% methanol retarded the reaction rate entirely; enzymes are known to lose their catalytic activity when the concentration of an organic co-solvent becomes too high.[9] A 15% methanol-buffer mixture optimized both the rate of the reaction and the e.e.

The use of the allyl group now provided an effective, non-chromatographic means for separation of the two esters. Deblockage of the remaining allyl ester with catalytic tetrakis(triphenylphosphine)palladium[10] in the presence of morpholine in THF provided the (*S*)-acid in >97% ee (Scheme 1, path b).[11]

Table 2: Results of the transesterification of substituted 2-arylpropionic acids.

Ester (1)	R	X	time(d)	% ee of (*S*)-2[7]	$[\alpha]^{25}_D$ of (*S*)-2[a]	% (*S*)-1 remaining
f	allyl	H	1.4	99	+ 72.8°	47
g	allyl	2-Me	3.0	96.9	+ 87.9°	44.4
h	allyl	2-OMe	0.85	97	+ 71.8°	44.8
e	allyl	2-I	1.0	97.4	+ 72.2°	43.6
i	allyl	4-OMe	1.8	87.6	+ 50.7°	45.2
j	allyl	4-NO_2	6.2	23	+ 19.5°	43.3
k	allyl	4-*iso*-butyl	15			

a)- All rotations were taken in chloroform (c = 1) except 2i which was taken in MeOH (c = 1).

Due to the success of the transesterification of allyl 2-(2-iodophenyl)propionate, the generality of the method was investigated (see Table 2). In all cases, the *S* -enantiomer remained as the allyl ester. As illustrated in Table 2, RLE was most effective with the unsubstituted and ortho-substituted systems. Substituents in the 4-position hampered the fit with the enzyme as evidenced by the decrease in the rate and e.e. This effect was shown to be largely steric rather than electronic in nature. The allyl ester of ibuprofen(**1k**), which has the largest steric bulk in the 4-position, did not transesterify under the reaction conditions. Apparently, no direct correlation can be made between the electronic nature of the substituents and the e.e. of the products. This novel method of transesterification can also be extended to 2-(2-iodophenyl)butyric acid affording the *S*-(+) enantiomer in >97% e.e.[12] While the rate of reaction was slightly slower with this compound, the increased length of the alkyl group did not affect the optical purity of the *S*-enantiomer.

This highly effective and novel enzymatic resolution of ortho-substituted arylpropanoic acids with rabbit liver esterase is a significant addition to the growing list of methods for preparing important organic intermediates and products in high optical purity. To the best of our knowledge this is the first reported use of RLE for this purpose. By using the enzyme's propensity for solvolysis of the *R*-enantiomer of the ester, the corresponding acid can be isolated in either the *S* - or *R*- form in high optical purity. The selective hydrolysis in water or transesterification in methanol-water followed by selective deblockage of the allyl ester provide a straightforward separation of the enantiomers.

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12. In this case, 50.9 units RLE/mmol ester were used. After 4 days the reaction had progressed to the 55% completion.

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