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Enantioselective synthesis of 2-hydroxy-1-indanone, a key precursor of enantiomerically pure 1-amino-2-indanol

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Abstract

Enantiomerically pure (*R*)- or (*S*)-2-hydroxy-1-indanone was synthesized by enzymatic kinetic resolution of racemic 2-acetoxy-1-indanone through hydrolysis or transesterification.

Enantiomerically pure 1-amino-2-indanol **1** is a key precursor of the chiral ligand[1] **2** and the chiral auxiliary[2] **3** for asymmetric synthesis and an important component of Indinavir **4**, a potent inhibitor of the protease of human immunodeficiency virus[3] (HIV). We recently reported that **1** is readily derived from optically active 2-hydroxy-1-indanone **5** through oxime formation and diastereoselective hydrogenation.[4] Hereby **5** was prepared by intramolecular Friedel–Crafts reaction of (*R*)-2-acetoxy-3-phenylpropanoyl chloride which was derived from D-phenylalanine.

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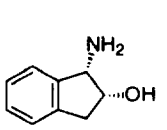

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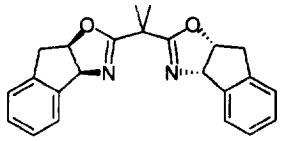

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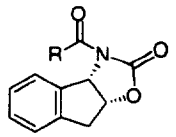

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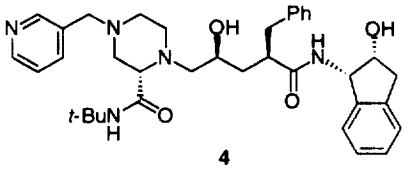

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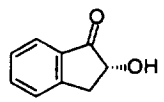
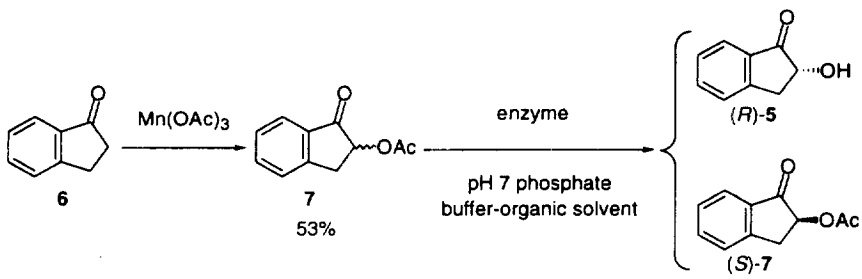


5

We report herein a facile resolution of 2-hydroxy-1-indanone **5**[5] by lipase through a kinetic resolution of the acetate of **5**. The whole process is outlined in Scheme 1.



6

7
53%

Scheme 1.

Oxidation of 1-indanone **6** with $Mn(OAc)_3$[6] afforded racemic acetate **7** in 53% yield. Although the enzyme-catalyzed kinetic resolution of secondary alcohols or their carboxylates has been well documented,[7] only a few examples are known concerning kinetic resolution of esters of α-keto alcohols.[8] For the enzymatic kinetic resolution of acetate **7**, we screened 84 commercially available hydrolases, including four acylases, one esterase, 54 lipases, and 25 proteases, in phosphate–MeOH buffer (pH 7) at room temperature. The tested acylases, esterase, and proteases exhibited low enantioselectivities ($E<10$),[9] whereas the lipases generally showed much better enantiomeric discrimination in favor of the *R*-isomer. Of these, seven lipases had an E value of over 15.[10] A second screening was performed in various organic solvent–phosphate buffer (pH 7) systems using three lipases that exhibited relatively high E and c values. The results are summarized in Table 1.

In all the solvents tested, the enzymes recognized preferentially the *R*-enantiomer of **7**. The best result, E=250, was obtained when Amano PS (*Pseudomonas* sp.) lipase was used in CH_3CN–phosphate buffer (pH 7). The enantioselectivity in the hydrolysis of **7** was strongly affected by the nature of the solvent but was independent of the hydrophobicity (log P) or polarity (ε) parameters of the organic solvent in contrast to the well-established correlation.[11]

We next examined transesterification of racemic **7** with 2-butanol, 1-pentanol, or 9-fluorenylmethanol in diisopropyl ether. The highest E value, 231, was obtained again using Amano PS lipase in a mixture of 1-pentanol and diisopropyl ether.[12] The enzyme preferentially transformed the *R*-enantiomer as was the case of hydrolysis in a buffer–organic solvent system.

Enzymatic hydrolysis of **7** was conducted in CH_3CN–phosphate buffer (pH 7) in the presence of Amano PS, under the conditions that afforded the highest E value. Treatment of racemic **7** (0.19 g) with Amano PS (95 mg) for 1 h at room temperature, followed by column chromatgraphy on silica gel,

Table 1
Enzymatic hydrolysis of 7 in a pH 7 phosphate buffer–co-solvent system

enzyme	co-solvent													
	MeOH		CH_3CN		EtOAc		THF		i-Pr_2O		dioxane		toluene	
	c	E	c	E	c	E	c	E	c	E	c	E	c	E
AMANO PS (*Pseudomonas sp.*)	0.37	75	0.32	250	0.20	168	0.28	178	0.42	159	0.48	108	0.20	219
MEITO QL (*Alcaligenes sp.*)	0.43	70	0.28	158	0.15	122	0.16	38	0.31	101	0.48	114	0.19	149
FLUKA 62312 (*Pseudomonas fluorescens*)	0.43	97	0.37	225	0.22	173	0.27	112	0.45	158	0.44	105	0.21	204

Conditions: A mixture of ester 7 (14 mg), enzyme (2 mg), a phosphate buffer (3.62 mL), and a co-solvent (1.21 mL) was stirred at 30 °C for 1 h, and the reaction was monitored by HPLC using DAICEL CHIRALCEL OB.
*The c value is the conversion degree and the E value is the ratio of the specificity constant of the two enantiomers calculated according to ref. 9.

afforded alcohol (*R*)-**5** (67 mg, 45% yield, 94% ee) and the recovered ester (*S*)-**7** (90 mg, 47% yield, 96% ee). Enantiomerically pure (*R*)-**5** was obtained after recrystallization from CH_2Cl_2–hexane (43 mg, 29% yield, >99% ee). *S*-Enriched ester **7** (94% ee) was hydrolyzed using $Sc(OTf)_3$ (20 mol%) to give rise to (*S*)-**5** without any loss of enantiomeric excess (59 mg, 84% yield) and thus enantiomerically pure (*S*)-**5** was obtained after recrystallization from CH_2Cl_2–hexane (42 mg, 60% yield, >99% ee).

In summary, enantiomerically pure *R*- and *S*-isomers of 2-hydroxy-1-indanone were obtained from racemic 2-acetoxy-1-indanone by a lipase-mediated kinetic resolution. The excellent enantiomeric discrimination allows us to isolate both enantiomers of 2-hydroxy-1-indanone in high yield and with high ee. This method provides an efficient route for the synthesis of enantiomerically pure 1-amino-2-indanol, a medicinally and chemically important compound. In addition, the present method will find wide applications to the synthesis of various optically active α-hydroxy ketones, which are versatile intermediates for natural products and useful stereodirecting groups.[13]

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