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Transesterification-based Enzymatic Resolutions of Racemic 3-Hydroxy-4-pentenylurethanes in Organic Solvents

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Abstract: An expedient synthesis of homochiral *N*-protected (*R*)- and (*S*)-3-hydroxy-4-pentenylamines (**1** and **2**) has been accomplished *via* the enzymatic resolution of the racemic **1** and **2** mediated by immobilized lipase in pentane.

Recent investigation in this laboratory has revealed that optically active *N*-protected 3-hydroxy-4-pentenylamines (**1** and **2**) serve as new and powerful chiral building blocks in the construction of hydroxylated alkaloids such as (-)-anisomycin,[1a] (-)-detoxinine,[1a] (+)-retronecine,[1b] (-)-supinidine,[1c] and 1-hydroxyindolizidines.[1d] Hitherto, optically active allylic alcohols **1** and **2** have been resolved by the Katsuki-Sharpless asymmetric epoxidation.[2] However, this methodology has some drawbacks: 1) The epoxides and the by-product pyrrolidines are concomitantly formed; 2) The completion of reaction requires a prolonged operation (7-14 days); 3) The procedure is inconvenient of work-up owing especially to laborious chromatographic fractionation of products; 4) The cost for large-scale preparation is not so inexpensive; 5) The values (89-92% ee) of enantiomeric excess are somewhat unsatisfactory. These detract from the overall utility of this method. Accordingly, we sought a procedure more efficient for the rapid production for greater quantities of optically pure urethanes **1** and **2**. Enzymes are now recognized as substrate-specific and highly enantioselective catalysts for asymmetric synthesis. In particular, lipases have recently been used for biocatalytic resolutions due to the admission of organic solvents as reaction media[3] and to the emergence of enol esters for essentially irreversible transfer of carboxylates.[4] In this letter, we disclose herein that racemic secondary allylic alcohols **1** and **2** can effectively be resolved *via* irreversible lipase-mediated transesterification in organic solvents.

Screening experiments were made with **1** using different lipases [*Pseudomonas* AK (Amano AK), *Pseudomonas* PS (Amano PS), *Candida rugosa* (Amano AY), *Porcine pancreas* (PPL), and *Candida cylindracea* (CCL)] and organic solvents. It was found that Amano AK, Amano PS, and PPL were selective in acylating the *S* isomer[5] of **1** whereas Amano AY and CCL acylated the *R* enantiomer faster than did its *S* antipode. A combination of Amano AK or Amano AY, vinyl acetate as acylation reagent, and pentane as organic solvent[6] gave the best results. The transesterfication of **2** was then undertaken. Of several lipases tested, it was found that Amano PS or Amano AY afforded the best result in terms of enantioselectivity as shown in Table 1.[7] The acetates (*S*)- or (*R*)-**3** and (*S*)- or (*R*)-**4** were readily converted with DIBALH into (*R*)- or (*S*)-**1** and (*R*)- or (*S*)-**2**, respectively, without loss of optical purity in good yields.

Furthermore, in order to improve the enantioselectivity, the use of the lipase in immobilized form[8] was examined. Fortunately, higher optical purities were performed as shown in Table 2. In addition, a shortening of the reaction period was concurrently achieved.

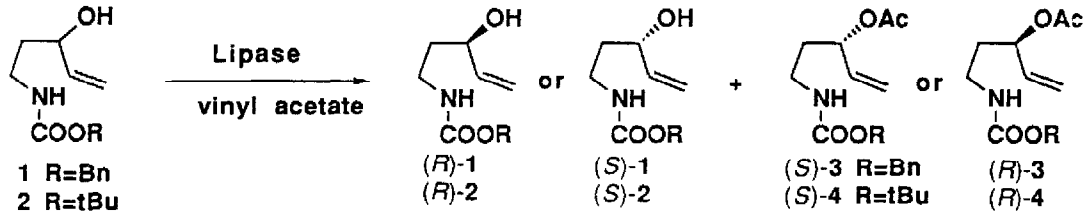

Table 1. Transesterification of 1 and 2 by lipases.

		condition[a]		alcohol (1,2)			acetate (3,4)			
entry	sub.	lipase	time(h)	yield(%)	ee(%)[b]	config.	yield(%)	ee(%)	config.	E[c]
1	1	AK	14	41	93	*R*	52	72	*S*	20
2	1	PS	14	45	35	*R*	52	54	*S*	5
3	1	PPL	89	90	6	*R*	1	6	*S*	1
4	1	CCL	67	78	16	*S*	16	78	*R*	9
5	1	AY	13	44	86	*S*	45	86	*R*	37
6	2	AK	18	46	37	*R*	52	33	*S*	3
7	2	PS	24	43	94	*R*	49	89	*S*	61
8	2	AY	46	58	53	*S*	29	95	*R*	66

a) All runs were conducted with 1 mmol of allyl alcohol , 5 eq. vinyl acetate, and 100 mg of lipase in pentane (5 mL) at 30 °C. b) Determined by ^{19}F NMR analysis of the derived (+)-MTPA ester. c) Chen, C.-S.; Fujimoto, G.; Girdaukas, G.; Sih, C.J. *J. Am Chem. Soc.* **1982**, *104*, 7294.

Table 2. Transesterification of 1 and 2 by the immobilized lipases.

		condition[a]		alcohol (1, 2)				acetate (3,4)			
entry	sub.	lipase	time(h)	yield(%)	ee(%)[b]	config.	$[\alpha]_D^{25}$	yield(%)	ee(%)	config.	E
1	1	AK	4	43	97	*R*	-2.98	49	77	*S*	31
2	1	AY	3	46	99	*S*	+3.05	46	96	*R*	265
3	2	PS	1.5	46	98	*R*	-9.87	51	85	*S*	57
4	2	AY	27	47	89	*S*	+8.95	48	87	*R*	43

a) All runs were conducted with 1 mmol of allyl alcohol , 5 eq. vinyl acetate, and 100 mg of lipase supported on Celite (400 mg) in pentane (5 mL) at 30 °C. b) Determined by ^{19}F NMR analysis of the derived (+)-MTPA ester.

This immobilized lipase-mediated resolution of secondary allylic alcohols **1** and **2** is superior in all respects to the Katsuki-Sharpless method. It was found that the asymmetric recognition for selective acylation depended on the lipase used. Such facile preparation of chirons are of obvious importance for contemporary asymmetric synthesis.[9] Extensions of this methodology to the resolution of other allylic alcohols are the subjects of active investigations, the results of which will be reported in due course.[10]

References and notes

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5. The similar enatio-discrimination has been observed; Burgess, K.; Jennings, L. D. *J. Am. Chem. Soc.* **1991**, *113*, 6129.
6. Although several solvents (hexane, cyclohexane, CH_2Cl_2, i-Pr_2O, THF) were examined, pentane provided the best result.
7. Absolute configrations of **1** and **2** were determined by comparison with the signs of specific rotations reported.[1a,b]
8. Immobilized forms were prepared by absorption of lipase on Celite 535; Bianchi, D.; Cesti, P.; Battistel, E. *J. Org. Chem.* **1988**, *53*, 5531.
9. The present procedure is facile and simple in operation and can readily be scaled up.
10. Generous gift of lipase Amano AK, PS, and AY from Amano Pharmaceutical Co. is gratefully acknowledged.

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