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Enzymatic Resolution of *N,N*-Dialkyl-3-hydroxy-4-pentenamides, Unsuccessful in Resolution by the Katsuki-Sharpless Asymmetric Epoxidation

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Abstract: An immobilized lipase-mediated resolution of secondary allylic alcohols **1** and **2** with which the Katsuki-Sharpless asymmetric epoxidation is unsuccessful is described.

The protocol based on the Katsuki-Sharpless asymmetric epoxidation provides an extremely valuable kinetic resolution of secondary allylic alcohols.[1] However, this resolution has some drawbacks: 1) Considerable difficulties have been encountered in the resolution of particular allylic alcohols; 2) The operation is inconvenient because of its laborious workup including tedious chromatographic fractionation; 3) The cost for large amounts of material is expensive. In practice, the Katsuki-Sharpless kinetic resolution is unsuccessful with *N,N*-dialkyl-3-hydroxy-4-pentenamides **1** and **2** and results in recovery of the starting materials, presumably because of a difficulty associated with the formation of an intramolecular hydrogen bond around the 3-hydroxyl group. Recently, the biocatalytic resolution of alcohols mediated by lipases has emerged as convenient procedures for optically active alcohols owing to the following features; simple procedures including non-rigorous reaction conditions such as those at room temperature and under an ordinary atmosphere; easy workup involving removal of the catalysts by filtration; facile separation of the products by simple chromatography; ready extension to a large scale experiment; ready accessibility of the catalysts at low cost.[2] Recent investigations in this laboratory have revealed that the transesterification-based enzymatic resolutions of *N*-(3-hydroxy-4-pentenyl)urethanes give excellent results in organic solvents.[3] In this communication, we disclose that racemic secondary allylic alcohols **1** and **2** can effectively be resolved *via* immobilized lipase-mediated transesterification.

Based on our previous work,[3] several lipases [*Pseudomonas* PS (Amano PS), *Pseudomonas* AK (Amano Ak), and *Cadida rugosa* (Amano AY)] and their immobilized forms[4] were examined for the transesterification of **1** and **2** using vinyl acetate in pentane. The results are summarized in Table. It was found that Amano PS and Amano AK were very effective and selective in acylating the *S* enantiomer whereas Amano AY was ineffective for asymmetric recognition. Both high enantioselectivity and shortening of the reaction period have been concurrently achieved by the use of the lipases in immobilized form. The use of the immobilized Amano PS gave the best results (entries 4 and 10).

The absolute configuration of the resolved allylic alcohols was determined by conversion of the acetates (*S*)-**3** and **4** to the known (3*S*,4*R*)-di-*O*-acetyl-2-deoxy-D-ribono-1,4-lactone (**5**)[5] using oxylactonization as shown in Scheme. Hydrolysis of (*S*)-**3** and **4** followed by *tert*-butyldimethlslylation of the resulting alcohols provided the amides **6** and **7**, respectively. Stereoselective oxylactonization of **6** with m-CPBA gave *trans*-lactone **8** and *cis*-lactone **9** in a 3.3:1 ratio. Similarly, the oxylactonization of **7** provided **8** and **9** in a 2.8:1 ratio. The *trans*-lactone **8** was desilylated with pyridinium *p*-toluenesulfonate[6] to afford the lactone-diol **10**, which was acetylated to give the diacetate **5** [$[\alpha]^{25}_{D}$ -5.31 (*c* 1.25 EtOH) lit.[5] $[\alpha]^{25}_{D}$ -5.20 (*c* 0.93 EtOH)].

1 R^1=Me, R^2=Bn
2 R^1=R^2=Bn

(*R*)-1 R^1=Me, R^2=Bn
(*R*)-2 R^1=R^2=Bn

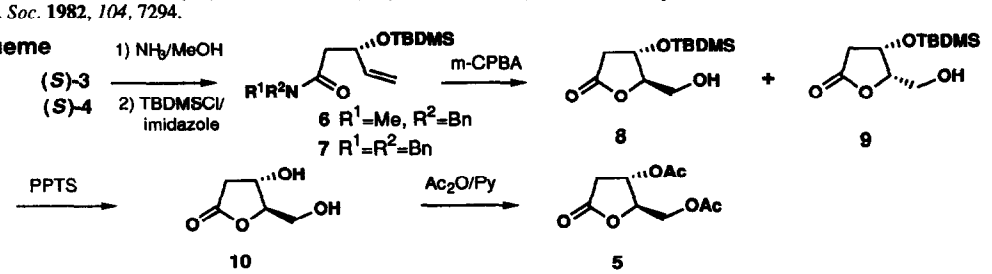
(*S*)-3 R^1=Me, R^2=Bn
(*S*)-4 R^1=R^2=Bn

Table. Transesterification of **1** and **2** by lipases.

		condition[a]		alcohol (**1**,**2**)			acetate (**3**,**4**)			
entry	sub.	lipase[b]	time(h)	yield(%)	ee(%)[c]	config.	yield(%)	ee(%)[c]	config.	E[d]
1	**1**	AK	48	47	89	*R*	49	87	*S*	43
2	**1**	AK(I)	24	36	97	*R*	46	93	*S*	116
3	**1**	PS	37	41	90	*R*	45	91	*S*	65
4	**1**	PS(I)	15	44	99	*R*	49	98	*S*	525
5	**1**	AY	73	64	7	*R*	30	20	*S*	2
6	**1**	AY(I)	95	80	2	*R*	11	71	*S*	6
7	**2**	AK	50	42	77	*R*	45	99	*S*	466
8	**2**	AK(I)	24	42	86	*R*	48	99	*S*	556
9	**2**	PS	50	47	98	*R*	48	98	*S*	458
10	**2**	PS(I)	22	42	>99	*R*	45	>99	*S*	>1057

a) All runs were conducted with 1 mmol of allylic alcohol , 5 eq. vinyl acetate, and 100 mg of lipase or 100 mg of lipase supported on Celite (400mg) in pentane (5 mL) at 30 °C. b) (I) shows an abbreviation of immobilized form. c) Determined by HPLC analysis using Daicel chiral column (AS) for **1** and **3**, and (AD) for **2** and **4**). d) Chen, C.-S.; Fujimoto, G.; Girdaukas, G.; Sih, C.J. *J. Am Chem. Soc.* **1982**, *104*, 7294.

Scheme



In summary, this immobilized lipase-mediated resolution of secondary allylic alchols **1** and **2**, unsuccessful in resolution by the Katsuki-Sharpless asymmetric epoxidation, is practically achieved. It was known that the iodolactonization of racemic *N*,*N*-dialkyl-3-hydroxy-4-pentenamides provided stereoselectively the functionalized *cis*-iodolactones.[7] Accordingly, the homochiral **1** and **2** thus resolved should be served as chirons for the synthesis of related biologically active compounds such as pheromone and flavor lactones and the results will be disclosed in due course.[8]

References and Notes

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8. Generous gift of lipases Amano AK, PS, and AY from Amano Pharmaceutical Co. is gratefully acknowledged.