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LIPASE CATALYZED ENANTIOSELECTIVE HYDROLYSIS OF 2-METHYL 3-ACETOXY ESTERS

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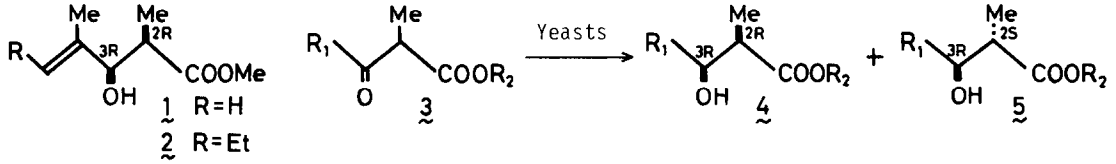
Summary: Highly enantioselective hydrolyses of syn-3-acetoxy-2-methyl ester and anti-3-acetoxy-2-methyl esters with lipase "Amano A" and lipase "Amano A-6" isolated from Aspergillus niger, are described.

In the synthetic studies of erythronolide A, it was required to prepare (2R,3R)-2,4-dimethyl-3-hydroxy-4-pentenoate 1 and -4-hexenoate 2.[1] As a model study, hoping to develop a general method for the synthesis of optically active erythro-2-methyl-3-hydroxy propionate derivatives, we examined an enantioselective reduction of 2-methyl-3-oxopropionate 3 having functionality at C-3 position by the use of various yeasts. The desired (2R,3R)-compound 4 was obtained along with C-2 isomer 5 with excellent optical purity (>99% e.e.) in cases where R_1 are 2-furyl[2] and ethoxycarbonyl group.[3]



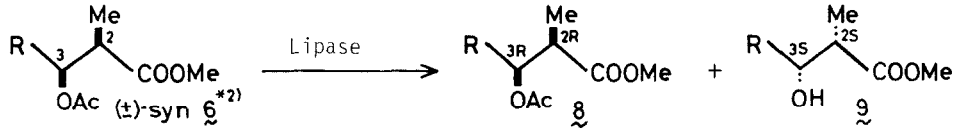
Unfortunately, however, every attempt to synthesize 1 and 2 by the above method failed. Since several steps are required for conversion of 2-furyl or ethoxycarbonyl groups into the desired olefinic functionalities, the present reductive method seemed not to be advisable for the synthesis of 1 and 2 and thus development of other direct methods were desired.

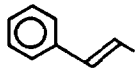
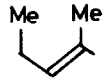
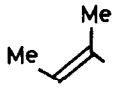
Recently, a number of reports have been published for preparation of chiral alcohols via enantioselective hydrolysis of the corresponding esters with microorganisms or enzymes.[4] Particularly, kinetic resolution of (±)-1 with Gliocladium roseum reported by Sih et al.[5] was quite suggestive for us. However, for preparative scale experiments, the use of commercially available, industrialized enzyme is preferable. Recent reports by Kanegafuchi group[6] concerning enzymatic preparation of (S)-5-hydroxymethyl-3-alkyl-2-oxazolidinones, an important intermediate for (S)-β-blockers, represent an excellent example of enzymes being used for large scale production. We now report lipase catalyzed chemo- and enantioselective kinetic resolution of (±)-methyl syn- and anti-2-methyl-3-acetoxy propionate derivative 6 and 7. The relative configurations of 2-methyl and 3-acetoxy groups in the substrates should be fixed to syn-(±)-6 or anti-(±)-7. Synthesis of syn-isomers can be achieved without any difficulties since we have previously[7] developed that $Zn(BH_4)_2$ reduction of the corresponding 3-keto esters produces syn-2-methyl-3-hydroxy esters with high stereoselectivity. Using this technique, compounds (±)-6a,[2] b,[8] c,[9] d,[cf 7] e,[cf 7] f[cf 7] were synthesized. Small amounts of anti-isomers produced in these substrates could be removed cleanly by SiO_2 column chromatography. On the other hand, anti-isomers (±)-7a,b,c had to be prepared by repeated SiO_2 column chromato-

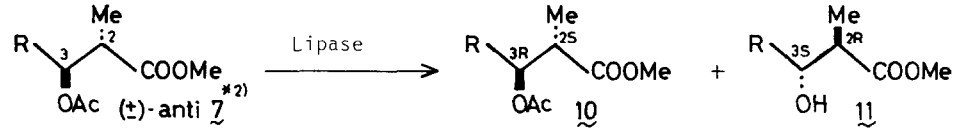
graphy of the 1:1 mixture of syn- and anti-isomers produced by Reformatsky reaction of the corresponding aldehydes and methyl 2-bromopropionate.

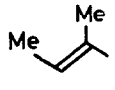
Initially, 2-furyl acetate (±)-6a was subjected to screening experiments using ten kinds of commercially available lipases. Among these, lipase "Amano A" and lipase "Amano A-6"

Table 1. Lipase Catalyzed Kinetic Resolution*1) of (±)-syn 6 and (±)-anti 7



substrate(R)	entry	lipase	time(hr)	yield(%) 8	yield(%) 9	optical purity(% e.e.) 8	optical purity(% e.e.) 9
a; 	1	Amano A	5	a; 42	43	90	80
	2	Amano A	8	33	56	>99	66
	3	Amano A-6	3	43	42	79	91
	4	Amano A-6	6.5	28	57	>99	47
b; 	5	Amano A	8	b; 42	54	93	71
	6	Amano A-6	8	35	64	91	47
c; 	7	Amano A	24	c(2R,3S); 60	c(2S,3R); 33	54	95
	8	Amano A-6	24	51	34	79	90
d; 	9	Amano A	24	d; 56	39	52	78
	10	Amano A-6	24	42	45	83	64
e; 	11	Amano A	27	e; 38	51	>99	64
	12	Amano A-6	27	27	61	>99	38
f; 	13	Amano A	24	f; 37	40	88	71
	14	Amano A-6	8	45	32	69	80



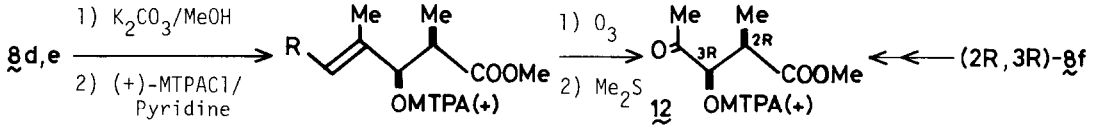
substrate(R)	entry	lipase	time(hr)	yield(%) 10	yield(%) 11	optical purity(% e.e.) 10	optical purity(% e.e.) 11
a; 	15	Amano A	6.5	a; 32	51	98	75
	16	Amano A-6	6	27	54	98	65
b; 	17	Amano A	8	b; 47	53	>99	85
	18	Amano A-6	8	45	55	>99	80
c; 	19	Amano A	28	c; 50	41	71	>99
	20	Amano A-6	28	44	51	>99	79

*1) The reaction conditions were not optimized.

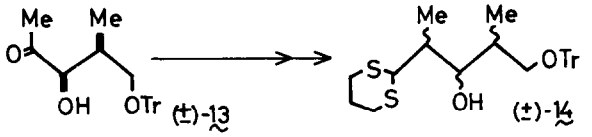
*2) Only one enantiomer (for (±)-syn 6 or (±)-anti 7) is shown.

from Aspergillus niger were found to hydrolyze (3S)-acetate selectively in the presence of methoxycarbonyl group in the same molecule and thus using these two enzymes enantioselective hydrolyses of other substrates were examined. Typical procedures are as follows: a solution of each substrate (ca. 100 mg) in 0.1 M phosphate buffer (pH 7.25, 20 ml) was incubated with lipase (ca. 50 mg) at 33°C for 3-28 hr. Progress of the reaction was monitored by TLC and when the spots due to esters and alcohols became the same size, reactions were stopped. The mixture was extracted with ether and separated by SiO_2 column chromatography. Results were shown in Table 1.

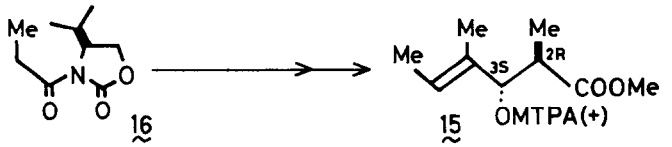
Absolute structures and optical purities of the products from 6a,b,c and 7a,b were determined in comparison of NMR data (400 MHz) of the corresponding C_3-(+)-MTPA esters with those of authentic samples.[2,8,10] The hydrolyzed product 9f ($[\alpha]_D^{20}$ -16.8° (c=5, $CHCl_3$) from (±)-6f (entry 14)) was shown to be (2S,3S)-isomer by the comparison with the known (2R,3R)-2,4-dimethl-3-hydroxy-4-pentenoate ($[\alpha]_D^{25}$ +19°, e.e.=0.95)[5] and thus unchanged ester 8f was determined as (2R,3R)-isomer. The absolute structures of 8d and 8e (2R,3R) were established by the comparison of NMR data (400 MHz) of keto alcohol (+)-MTPA ester 12 derived from 8d,e with those of 12 derived from 8f of (2R,3R)-structure.



It should be noted that no epimerization was observed during ozonolysis (for example, 8f, 88% e.e.; 12 from 8f, 89% e.e.). Thus, as (±)-13, structually related to (2R,3R)-12, has already been converted into four possible diastereomers (±)-14 having functionalized 1,3-dimethyl-2-hydroxy unit in this laboratory,[11] the present results means that the route for the synthesis of the corresponding optically active compounds 14 were newly opened.



The absolute configuration of 11c was established as (2R,3S) by the comparison of NMR data (400 MHz) with those of the authentic sample 15 prepared from 16 by the method of Evans et al.[12]



Optical purity of the chiral products from (±)-6 were all determined based on the NMR data (400 MHz) as described in the previous paper.[cf. 2, 13]

From the results shown in Table 1, industrialized enzymes, lipase "Amano A" and lipase "Amano A-6", were found to be used effectively in kinetic resolution of (±)-6 and (±)-7. (3S)-Acetates were hydrolyzed more rapidly than (3R)-acetates irrespective of the configuration at C-2 Me group and far more rapidly than methoxycarbonyl group. The desired (2R,3R)-esters 8 were usually produced in high optical purity.[14] Kinetic resolution experiments can be carried out using substantial amounts of the substrates. In fact, when 1 g of (±)-6d was treated with lipase "Amano A-6" (500 mg), 8d (reaction time, 28 hr, optical purity, 92% e.e.

in this case)[14] was obtained in 38% yield.

It should be emphasized that development of the present method for the syntheses of optically active synthons having two chiral centers became possible only in combination with an excellent method for the syntheses of (±)-substrate having stereochemically well defined substituents. This type of collaboration of chemical and biological means should be increasingly important in the near future.

Syntheses of (-)-oudemansin A have been achieved using 8a[15] and 8c.[10] Synthesis of Erythronolide A is now in progress using 8d and 8f prepared by Evans's method.[12] Hereafter, these optically active synthons will be supplied much easily than before by the present method. Synthesis of other polyoxygenated natural products are being undertaken.

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