Tetrahedron: Asymmetry Vol. 4, No. 11, pp. 2303-2306, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
Pergamon Press Ltd

OXALATE AS AN ACTIVATED ESTER GROUP IN LIPASE-CATALYZED ENANTIOSELECTIVE HYDROLYSIS: A VERSATILE APPROACH TO *d*-α-TOCOPHEROL

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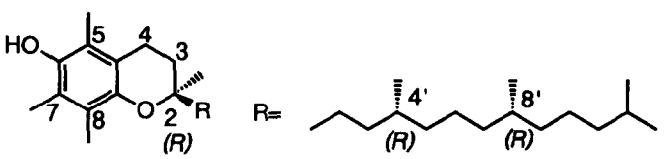
(*Received in Japan* 16 *August* 1993)

Abstract; The *d*-α-tocopherol was synthesized effectively by enzyme-catalyzed enantioselective hydrolysis of *dl*-α-tocopherol oxalate. The enzymes can recognize a stereogenic carbon atom remote from the reaction site.

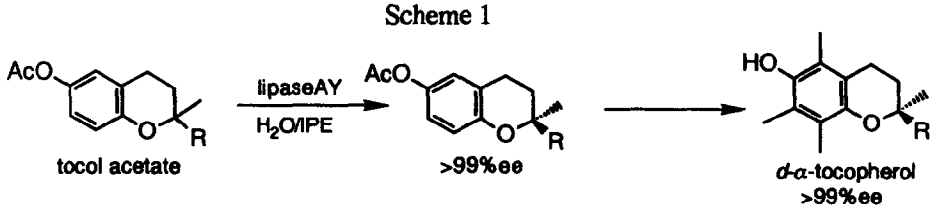
The α-tocopherol is known as a potent, safe, and lipid-soluble antioxidant. Recently, tocopherol and super oxide dismutase(SOD) and other antioxidants are attracting attention as scavengers of super oxide series.[1] As tocopherol is being used for various purposes, in the future, demand will increase. Presently, the majority of tocopherol is being used as a mixture of its eight isomers, which have been reported to show different biological activities.[2] Tocopherol as a medicine would best be used as a single isomer, and accordingly we have investigated the effective synthesis of *d*-α-tocopherol using an enzyme-catalyzed kinetic resolution.



d-α-Tocopherol [*(R)*-1]

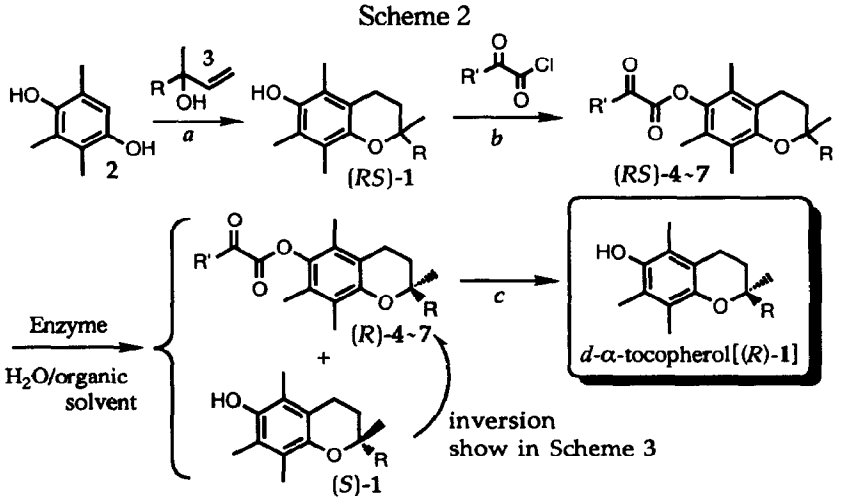
Previously, we reported the unsuccessful lipase-catalyzed hydrolysis of *dl*-α-tocopherol(2*RS*,4'*R*,8'*R*) acetate and benzoate, and accordingly, tocol acetate was chosen as a less sterically hindered substrate for lipase-catalyzed hydrolysis. This approach was successful to give (*R*)-tocol acetate in high enantiomeric purity, which was converted to *d*-α-tocopherol (Scheme 1).[3]

Scheme 1



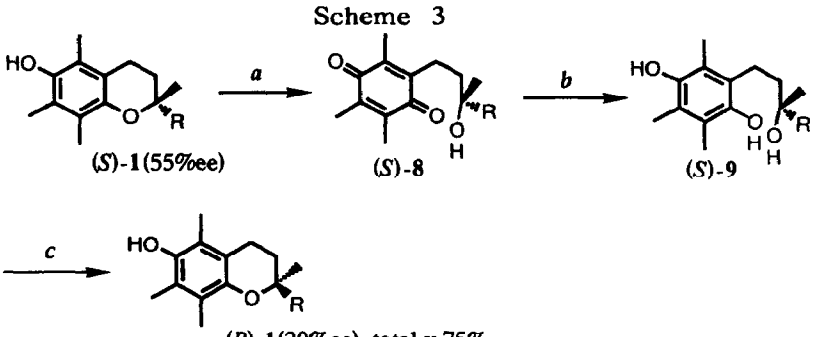
In this paper, we describe a novel resolution of *dl*-α-tocopherol itself using the lipase-catalyzed hydrolysis in order to establish most effective synthesis of *d*-α-tocopherol. After examination, oxalates were found to be activated ester groups in lipase-catalyzed enantioselective hydrolysis of *dl*-α-tocopherol.

Scheme 2



Reagents; *a*: BF_3/Et_2O *b*: Et_3N/THF *c*: NaOH/MeOH.

Scheme 3

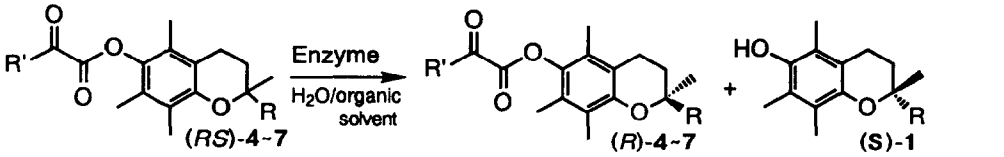


Reagents; *a*: $FeCl_3$/MeOH,H_2O *b*: H_2,Pd-C/Et_2O *c*: BF_3/Et_2O

The *dl*-α-tocopherol oxalates(*RS*)-4~7 were synthesized as shown in Scheme 2. The results of lipase-catalyzed hydrolyses of (*RS*)-4~7 are listed in Table 1. The tocopherol oxalyl amide[4] was hydrolyzed with good enantioselectivity (81%ee and 80%ee) by lipaseAY(*Candida rugosa*) or lipaseOF(*Candida cylindrasea*) respectively, in water-saturated IPE (entries 13 and 14). Hydrolysis of the thus obtained (*R*)-tocopherol oxalyl amide with NaOH afforded *d*-α-tocopherol without racemization.[5]

Table 1

Enantioselective synthesis of d-α-Tocopherol by lipase-catalyzed hydrolysis [a]



Entry	R'		Enzyme[d]	Sol.	Time	C.Y.[b]	%ee[c]	C.Y.[b]	%ee[c]
1	CH_3O		AY	IPE	1h	27	17(R)	72	15(S)
2	CH_3O	4	OF	IPE	1.5h	60	6(R)	26	35(S)
3	CH_3O		AY	cyclohexane	2.5h	36	17(R)	54	35(S)
4	CH_3O		OF	cyclohexane	4h	68	9(R)	18	35(S)
5	C_2H_5O		AY	IPE	24h	20	13(R)	72	12(S)
6	C_2H_5O	5	OF	IPE	4h	73	4(R)	21	35(S)
7	C_2H_5O		AY	cyclohexane	18h	55	20(R)	31	36(S)
8	C_2H_5O		OF	cyclohexane	24h	69	1(R)	14	43(S)
9	^tBuO		AY	IPE	2d	45	18(R)	46	38(S)
10	^tBuO	6	OF	IPE	11d	67	11(R)	33	42(S)
11	^tBuO		AY	cyclohexane	3d	47	36(R)	33	35(S)
12	^tBuO		OF	cyclohexane	10d	63	8(R)	30	45(S)
13	H_2N		AY	IPE	2.5d	28	81(R)	61	48(S)
14	H_2N	7	OF	IPE	2.5d	41	80(R)	48	55(S)
15	H_2N		AY	cyclohexane	3d	61	18(R)	31	43(S)
16	H_2N		OF	cyclohexane	3d	63	6(R)	28	45(S)

a All reactions were carried out by stirring a mixture of substrate(50mg) lipase(50mg) and organic solvent saturated with water at 25°C. *b* Isolated yield. *c* Enantiomeric purities were determined by HPLC analyses using a column packed with Chiralcel OD-H (2-propanol/hexane=1/2000). *d* AY=Amano LipaseAY(*Candida rugosa*),OF=Meito LipaseOF (*Candida cylindrasea*).

The unnatural enantiomer (*S*)-**1**(55%ee) was converted to *d*-α-tocopherol (20%ee) in a total yield of 75% in three steps according to the method of Schudel *et al.*[6] (Scheme 3). Oxalation of the *d*-α-tocopherol thus obtained gave the substrate for the repeated lipase-catalyzed hydrolysis. It is an interesting result that tocopherol oxalates are resolved with moderate selectivity by lipaseAY or OF in spite of the reaction site being fairly remote from the

stereogenic carbon atom.[7] This oxalate strategy is applicable to other types of substrate for lipase-catalyzed enantioselective hydrolysis.

Acknowledgement

This work was partly supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Japan (No. 05403032)

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4. (*RS*)-**7**: ^{1}H-NMR ($CDCl_3$) δ: 0.83–0.90(12H,m), 1.00-1.65(24H,m), 1.70-1.89(2H,m), 2.06-2.13(9H,m), 2.60(2H,t,J=6Hz).
5. Identification was carried out by comparison of HPLC analysis using a column packed with Daicel Chiralcel OD-H (2-propanol/hexane=1/2000) with an authentic *d*-α-tocopherol. (R)-**1**: ^{1}H-NMR ($CDCl_3$) δ: 0.83-0.88(12H,m), 1.00-1.59(24H,m), 1.73-1.88(2H,m), 2.11(6H,s), 2.16(3H,s), 2.60(2H,m), 4.16(1H,s). MASS: m/z(M^+)430.
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