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Total Synthesis of (-)-Oudemansin X Based on Enzymatic Resolution Using Immobilized Lipase

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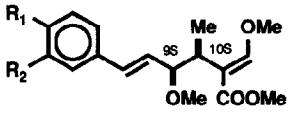
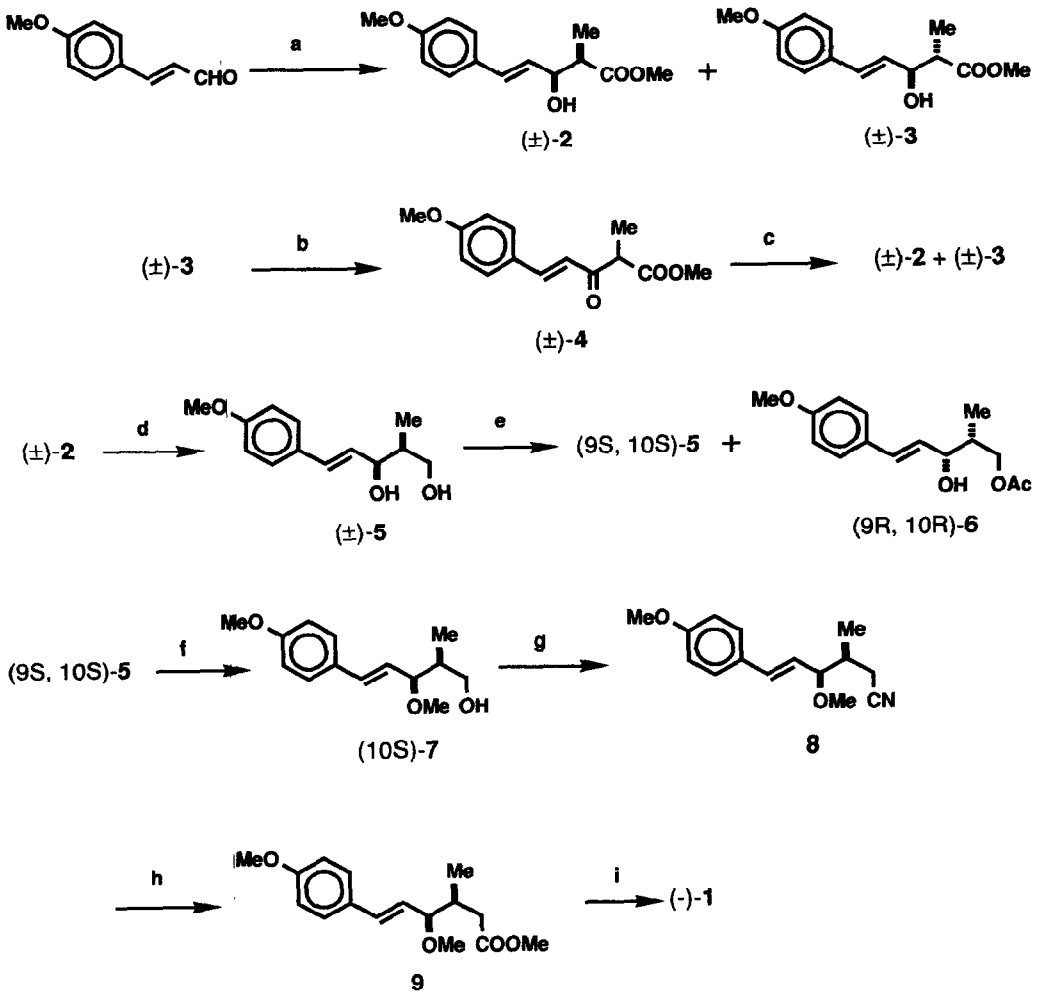
Abstract: (-)-Oudemansin X (**1**) was synthesized based on enzymatic resolution of (±)-diol **5** using immobilized lipase.

Oudemansin X (**1**), an antibiotic isolated from mycelial cultures of *Oudemansiella radicata* exhibits strong antifungal activities[1]. The total synthesis of (-)-**1** has already been achieved from an optically active cyclitol, L-quebrachitol[2]. In the previously reported chiral syntheses of oudemansin A[3] and B[4] similar to oudemansin X (**1**), synthetic chiral intermediates were obtained by the microbiological asymmetric reduction of the α-methyl-β-keto ester or α-chloroacetoacetate. We now report that **1** was synthesized in optically active form (-)-**1** based on enzymatic resolution using immobilized lipase in organic solvent.



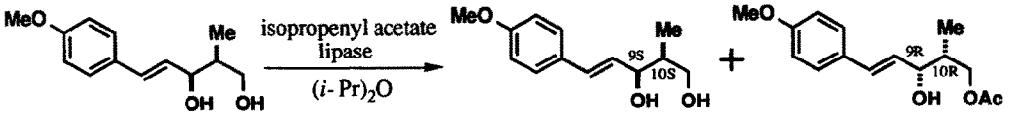
R_1 = OMe, R_2 = H	Oudemansin X (**1**)
R_1 = R_2 = H	Oudemansin A
R_1 = Cl, R_2 = OMe	Oudemansin B

The most intriguing point of the present synthesis is the preparation of the optically active diol **5**. This was successfully achieved by carring out an enantioselective monoacetylation of (±)-diol **5** using immobilized lipase. Reformatsky reaction of *p*-methoxy-cinnamaldehyde and methyl α-bromopropanoate gave (±)-**2**[5] (50%) and (±)-**3**[8] (42%). Oxidation of (±)-**3** with DDQ provided (±)-β-keto ester **4** (72%), which was reduced with $Zn(BH_4)_2$ to give the (±)-*syn*-**2** (14%) along with a small amount of the (±)-*anti*-**3** (2%)[6]. As $Zn(BH_4)_2$ reduction of α-methyl-β-keto ester was reported to give predominantly the *syn*-α-methyl-β-hydroxy ester[7], the relative structure of the present (±)-**2** was assigned the *syn*-structure. Reduction of (±)-**2** with $LiBH_4$ provided (±)-*syn* diol **5** in 96% yield. Initially, (±)-**5** was subjected to screening experiments using seven kinds of commercially available lipases. Among them, lipase "Amano P" from *Pseudomonas* sp. was found to give the (9R, 10R)-mono acetate **6** (68%, 43%ee) and the unchanged (9S, 10S)-diol **5** (31%, 92%ee) in the presence of isopropenyl acetate as an acyl donor in isopropyl ether as shown in table (entry 7). Then immobilized lipase "Amano P" was obtained by illumination of a mixture consisting of a photo-crosslinkable resin prepolymer ENTP-4000[9], a photo-sensitizer such as benzoin ethyl ether and the crude lipase "Amano P". When (±)-**5** was subjected to the enantioselective acetylation using immobilized lipase for long time (16hr, entry 8), 97%ee of (9S, 10S)-**5** was obtained in 27% yield, while short time (2~3hr, entry 9, 10) incubation gave 93~94%ee of (9R, 10R)-**6** in 23% yield. The recovered (9S, 10S)-**5** having 27% enantiomeric excess was again subjected to the enzymatic reaction using the recovered immobilized lipase (entry 11) for 24hr to give (9S,



a; $CH_3CHBrCOOMe/Zn/PhH$, reflux b; DDQ/THF, 0°C c; $Zn(BH_4)_2/Et_2O$, 0°C
d; $LiBH_4$/THF, 0°C e; isopropenyl acetate/lipase
f; 1) $^tBuMe_2SiCl$/imidazole/DMF 2) MeI/KH/THF 3) $Bu_4N^+F^-$/THF
g; 1) CBr_4/Ph_3P 2) NaCN/DMSO h; 1) OH^- 2) H^+ 3) CH_2N_2
i; 1) HCOOMe/LDA/THF, -78°C~0°C 2) OH^- 3) H^+ 4) CH_2N_2/MeOH

Table



(±)-**5** (9S,10S)-**5** (9R,10R)-**6**

Entry	Substrate (mg)	Lipase	Time (hr)	Product (9S,10S)-5		(9R,10R)-6	
				%	(%ee)	%	(%ee)
1	100	Nagase P (*Pseudomonas* sp.)	72	57	(14)	35	(44)
2	100	B-4 (*Rhizopus japonicus*)	72	50	(29)	43	(49)
3	100	My-30 (*Candida cylindracea*)	8	39	(34)	27	(25)
4	100	PL-266 (*Alcaligenes* sp.)	8	30	(88)	42	(5)
5	100	AL (*Achromobactor* sp.)	8	54	(24)	41	(37)
6	100	Amano AY-30 (*Candida rugosa*)	9	57	(5)	14	(37)
7	100	Amano P (*Pseudomonas* sp.)	6	31	(92)	68	(43)
8	100	Immobilized lipase (Amano P)	16	27	(97)	66	(42)
9	100	Immobilized lipase (Amano P)	2	70	(23)	23	(94)
10	200	Immobilized lipase (Amano P)	3	74	(27)	23	(93)
11*	300	Immobilized lipase (Amano P)	24	49	(88)	44	(41)

*) Optically active (9S,10S)-5 (27%ee) was employed

10S)-**5** (49% yield, 88%ee) and (9R, 10R)-**6** (44% yield, 41%ee). On one recrystallization of (9S, 10S)-**5** (88%ee), optically pure (>99%ee) (9S, 10S)-**5** ($[\alpha]_D$ +17.6, c=1.00, $CHCl_3$) was obtained. Optical purity of enzymatic reaction products was determined by HPLC on a CHIRALCEL OD (250 X 4.6 mm) column. In order to confirm the absolute structure of the present (+)-**5**, (+)-**5** was successfully converted to the reported compound (10S)-**8**[2,10]. Monosilylation of (+)-**5** followed by methylation gave the 9-methoxy silyl ether which was treated with fluoride ion to give the 9-methoxy alcohol (+)-**7** ($[\alpha]_D$ +43.2, c=1.00, $CHCl_3$) in 96% yield in three steps. Bromination of (+)-**7** followed by treatment of NaCN gave the 9-methoxy nitrile (-)-**8** ($[\alpha]_D$ -35.4, c=1.00, $CHCl_3$) in 91% overall yield, whose spectral data were identical with those ($[\alpha]_D$ -34.5, c=0.30, $CHCl_3$) of the reported (10S)-**8**. Thus the absolute structure of (+)-**5** was determined to be 9S, 10S and that of mono acetate **6** was confirmed to be 9R, 10R. Conversion of (10S)-methyl ester **9** was achieved by the standard procedure (three steps) in overall 83% yield. Formylation of (10S)-**9** with LDA and methyl formate in THF at -78°C to 0°C, followed by treatment with CH_2N_2-MeOH produced the optically active oudemansin X (**1**) (23% overall yield, $[\alpha]_D$ -20 (c=1.0, EtOH)) after purification by HPLC. The spectral data (IR, NMR, and $[\alpha]_D$) of the synthetic (-)-**1** was identical with those ($[\alpha]_D$ -20 (c=0.16, EtOH)) of synthetic natural oudemansin X (**1**)[2].

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References and Notes

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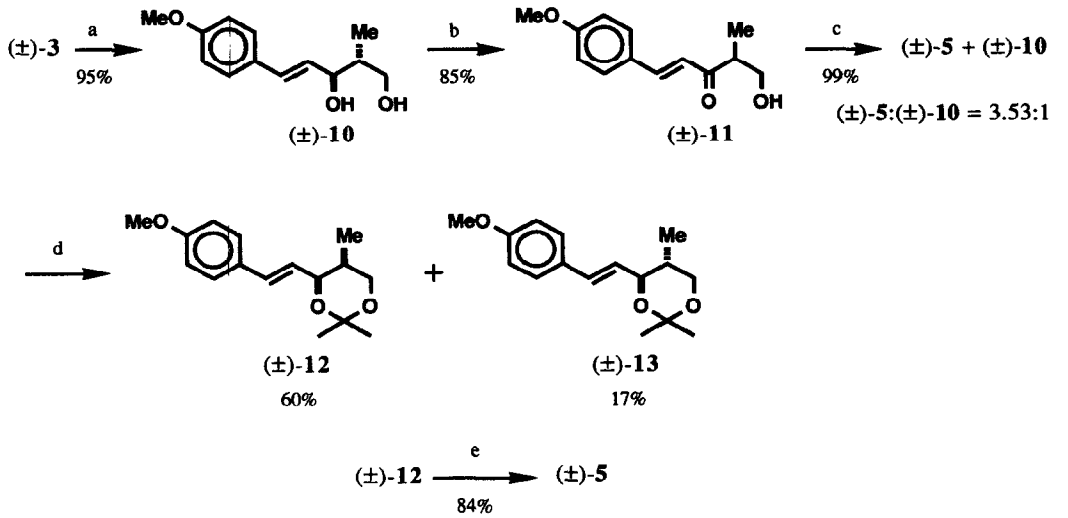
5) Satisfactory analytical data were obtained for all new compounds.
6) Reaction are not optimized yet. Depending upon the stability of reduction product, much higher yield is expected by changing workup and reaction conditions.
7) T. Nakata and T. Oishi, *Tetrahedron Lett.*, **21**, 1641 (1980).
8) The (±)-*anti* isomer **3** was successfully converted into the (±)-*syn* diol **5**.



a; $LiBH_4$/THF, 0°C b; DDQ/THF, 0°C c; $Zn(BH_4)_2/Et_2O$, 0°C
d; 1) $Me_2C(OMe)_2$/CSA/PhH, R.T. 2) separation e; PPTS/MeOH, R.T.

9) S. Fukui and A. Tanaka, *Advances in Biochemical Engineering/Biotechnology*, **29**, 1 (1984).
10) Private communication from Prof. S. Ogawa.