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The chemistry of Zerumbone IV Asymmetric synthesis of Zerumbol

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Abstract

The achiral sesquiterpene zerumbone (**1**), readily available from a wild ginger, has unique functionality and reactivity which make it a potential starting material for conversion to useful compounds such as paclitaxel, provided that it can easily be transformed to chiral derivatives. Optically active zerumbol **2** and its acetate **3** were synthesized by lipase-catalyzed stereoselective transesterification of racemic **2**. In the best conditions found, a lipase from *Pseudomonas fluorescens* (Amano AK) and isopropenyl acetate in THF at 30 °C afforded (*R*)-**2** and (*S*)-**3** with an *E* value of 56. The absolute configuration of (*R*)-**2** was determined by Sharpless epoxidation with L-diethyltartrate (L-DET) to a bisepoxide of known configuration.

Keywords: Zerumbone; Zerumbol; Asymmetric synthesis; Transesterification

1. Introduction

Zerumbone (**1**), the main component of the essential oil of a wild ginger, *Zingiber zerumbet* Smith [1], is a monocyclic sesquiterpene containing a cross-conjugated dienone system. It exhibits a variety of interesting reactions, e.g. regio- and stereoselective conjugate additions [2], transannular ring contraction [2] and cyclization [3], and several regiospecific reactions which cleave the 11-membered ring [4]. It was found that some of the new zerumbone derivatives possessed intriguing bioactivities [4,5]. Much of its chemistry remains to be explored in order to exploit the ready availability of this substance as a versatile starting material for conversion to other useful compounds. We have already noted [2], e.g. the possibility of employing zerumbone as a precursor of the potent anticancer agent paclitaxel. A prerequisite for the goal of reaching the paclitaxel family, with its complex array of chiral centers, is to introduce chirality into the achiral zerumbone skeleton. We have already achieved one solution to that problem by preparing an optically active bisepoxide from racemic zerumbol (**2**) in nearly 100% optical purity by the Sharpless asymmetric epoxidation [6]. However, remained optically active alcohol was not detected and decomposed in this case. This report addresses a second approach, the application of the

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lipase-catalyzed enantioselective transesterification of racemic (**2**). We find that optically active zerumbol (*R*)-**2** and zerumbyl acetate (*S*)-**3** can be readily obtained by lipase-catalyzed transesterification in the presence of the lipase from *Pseudomonas fluorescens* (Amano AK) enzyme system.

2. Results and discussion

Zerumbone (**1**) was reduced with lithium aluminum hydride to afford racemic zerumbol (**2**) in quantitative yield. The lipase-catalyzed kinetically transesterification of **2** was then investigated (Scheme 1).

Our previous work presented a guide for the selection of the solvent to be used in the lipase-catalyzed high-enantioselective transesterification. In many cases, *n*-propyl ether or diisopropyl ether (DIPE) were recommended [7], since the reciprocals of the dielectric constants of these solvents were approximately 0.3. Table 1 shows the results from the transesterification of **2** with vinyl acetate in DIPE in the presence of 15 lipases for 12 days. Three lipases (Amano AK, Amano GC, and Meito 266) produced the corresponding acetate in good conversion, along with unreacted substrate.

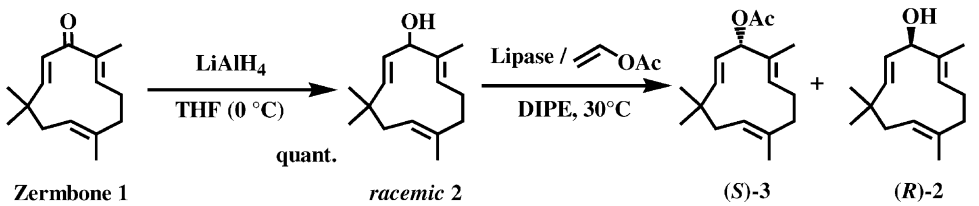
The transesterification of **2** with these three lipases was then studied in various solvents (Table 2). Of those tested, the stereoselectivity of the lipase-catalyzed transesterification was higher using DIPE or THF and the lipases Amano AK and Meito 266. The combination of Amano AK and THF gave the highest *E* value (enantiomeric ratio) [8], 28. One more variation in the conditions for lipase-catalyzed transesterification of **2** was investigated by substituting isopropenyl acetate for vinyl acetate in THF, using the three best lipases of the vinyl acetate study. As shown in Table 2, there was no reaction with Amano GC. The *E* value was the highest, 56, with Amano AK though the yield of **3** decreased sharply. The enantiomeric excess (ee) of optically active **2** and **3** could be determined by gas chromatography using an optically active capillary column of CPCD.

Table 1
Transesterification of **2** using various lipases in diisopropyl ether for 12 days

Lipase	Biological name	Conversion (%)
Amano AK	*Pseudomonas fluorescens*	12
Amano AY	*Candida rugosa*	5
Amano GC		34
Amano PS	*Pseudomonas* sp.	7
Meito 266		35
Meito MY	*Candida cylindracea*	8
Meito OF360		2
Amano A	*Aspergillus niger*	0
Amano M	*Mucor javanicus*	0
Amano R	*Penicillium roqueforti*	0
Meito AL	*Achromobacter* sp.	0
Meito PL	*Alcaligenes* sp.	0
PLE-A		0
Pancreatin F		0
PPL		0

Plots of the rates of formation of acetate **3** employing the lipases of Amano AK and Meito 266 in four solvents (DIPE, THF, AcOEt, and hexane) are shown in Fig. 1.

The reaction was slowest in the least polar solvent (hexane), and faster with Meito 266 than Amano AK. However, the enantioselectivity of the reaction was reduced in those transesterifications which proceeded rapidly. Consequently, the *E* value reached a maximum with the combination of the lipase, Amano AK, in a solvent of medium polarity, THF.



Scheme 1.

Table 2
E values of transesterification in various solvents

Lipase	Acetylation reagent	Solvents			
		DIPE	THF	AcOEt	Hexane
Amano AK	Vinyl acetate	23	28	22	1
Amano GC	Vinyl acetate	4	2	2	3
Meito 266	Vinyl acetate	10	19	3	1
Amano AK	Isopropenyl acetate		56		
Amano GC	Isopropenyl acetate		NR[a]		
Meito 266	Isopropenyl acetate		20		

[a] No reaction.

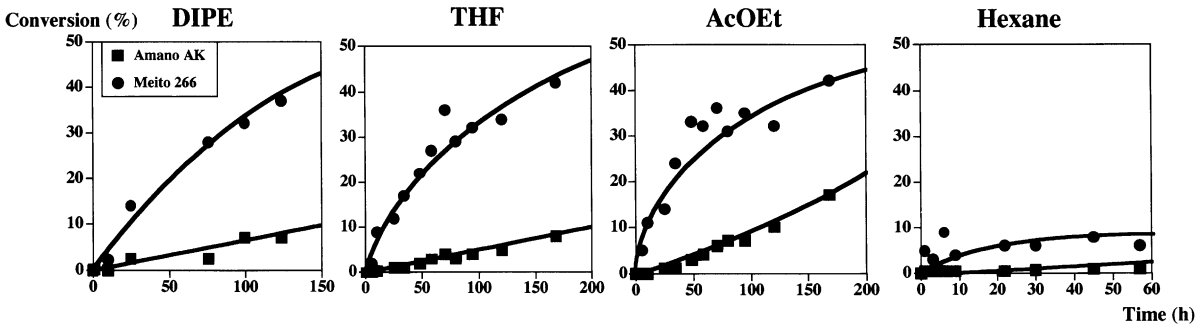
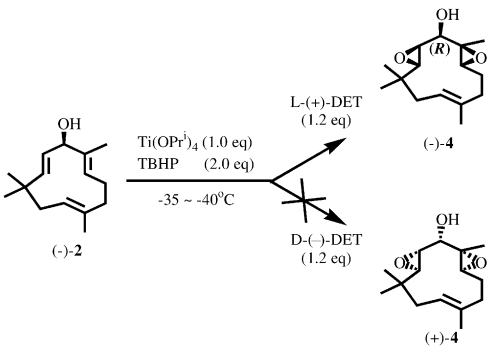


Fig. 1. Reaction rates of transesterification of zerumbol with vinyl acetate.

3. Absolute configuration

The absolute configuration of optically active **2** was determined by Sharpless asymmetric epoxidation to a bisepoxide of known configuration. We reported recently [6] that, using L-DET as a chiral auxiliary, racemic **2** was converted to a single bisepoxide (1*R*, 2*S*, 3*R*, 10*S*, 11*R*)-2,3-10,11-diepoxy-2,6,9,9-tetramethyl-6-cycloundecen-1-ol, (−)-**4**, whose absolute configuration was determined by single-crystal X-ray analysis of its *p*-chlorobenzoate. Use of the enantiomeric tartrate, D-DET, under the same conditions gave the antipode (+)-**4**. Sharpless epoxidation of (−)-**2**, recovered from the lipase-catalyzed transesterification, proceeded in the presence of L-DET to afford (−)-**4** although no epoxidation occurred in the presence of D-DET (Scheme 2). This correlation confirms that (−)-**2** has the (*R*) configuration and (+)-**3** is the (*S*) enantiomer.



Scheme 2.

4. Conclusion

An efficient route to both antipodes of optically active zerumbol was achieved enantioselectively by lipase-catalyzed transesterification using Amano AK and isopropenyl acetate in THF system. This finding opens the way to using this easily available terpene as a starting material for conversion to useful chiral products.

5. Experimental

5.1. Instruments

NMR spectra were recorded on spectrometer JEOL EX-270 at 270 MHz for ^{1}H and at 68 MHz for ^{13}C in $CDCl_3$ with TMS as the internal standard. IR spectra were recorded on a Shimadzu 8200D. Optical rotations were measured with a Horiba SEPA-300 polarimeter. High resolution mass were recorded on a JEOL The Tandem MStation JMS-700 TKM by direct injection at 70 eV. Gas chromatographic analyses were performed using a GL Science gas chromatograph Model GC 353 equipped with a TC-1 column or a chiral capillary column (CP-Cyclodextrin-B-236-M-19).

5.2. General procedure of lipase-catalyzed transesterification of zerumbol 2, (R)-2

A mixture of (±)-zerumbol 2 (20 mg, 0.091 mmol), isopropenyl acetate (0.93 g, 10.7 mmol), and the lipase (dry Amano AK, 250 mg) in THF (10 ml: water content = 1.0% v/v) was stirred for 12 h at 30 °C. The reaction was followed by gas chromatography using a column of TC-1 (detector and injection temperature, 200 °C; column temperature, 140 °C; carrier gas, N_2; FID detector). Under these conditions the retention time of zerumbol and its corresponding acetate were 6.1 min and 9.9 min, respectively. The reaction mixture was filtered and the filtrate was concentrated. Chromatography on silica gel, eluting with a 4:1 mixture of hexane and AcOEt, afforded (−)-zerumbol **2** and (+)-zerumbyl acetate **3** (7.0 mg, 29%) in 99% ee as determined by gas chromatography using a column of CPCD (column temperature, 120 °C; detector and injection temperature, 160 °C; carrier gas, N_2; FID detector). Under these conditions the retention times were: (*S*)-**2**, 99.8 min; (*R*)-**2**, 102.9 min; (*S*)-**3**, 121.0 min; (*R*)-**3**, 127.0 min.

5.3. Zerumbyl acetate *3*, *(S)-3*

$[\alpha]_D$ (23.5 °C) = +28.9 (EtOH, c = 0.125), IR (KBr) 2957, 1740, 1240 cm^{-1} ^{1}H NMR: δ 1.07 (s, 3H, CH_3 at C9), 1.08 (s, 3H, CH_3 at C9), 1.44 (s, 3H, CH_3 at C6), 1.63 (s, 3H, CH_3 at C2), 1.79 (dd, 1H, J = 4.29 and 13.85 Hz, H at C8), 2.06 (dd, 1H, J = 10.56 and 13.85 Hz, H at C8), 2.06 (s, 3H, CH_3 at CH_3CO), 2.10 (m, 2H, H at C5), 2.15 (m, 2H, H at C4), 4.84 (dd, 1H, J = 4.29 and 10.56 Hz, H at C7), 5.26 (t, 1H, J = 7.59 Hz, H at C3), 5.30 (d, 1H, J = 15.50 Hz, H at C10), 5.47 (d, 1H, J = 7.26 Hz, at C1), 5.54 (dd, 1H, J = 7.26 and 15.50 Hz, H at C11); ^{13}C NMR:δ 13.17 (CH_3 at C2), 15.02 (CH_3 at C6), 21.19 (CH_3 at CH_3CO), 23.04 (C4), 23.83 (CH_3 at C9), 29.51 (CH_3 at C9), 37.25 (C9), 39.21 (C5), 41.91 (C8), 79.95 (C1), 124.73 (C7), 127.10 (C3), 127.66 (C11), 133.23 (C6), 138.67 (C2), 140.83 (C10), 170.39 (CO). HRMS *m/z* calcd. mass for $C_{17}H_{26}0_2$ 262.1931, found 262.1922.

5.4. Sharpless epoxidation of (−)-zerumbol

A mixture of $Ti(OPr^i)_4$ (12.9 mg, 4.54×10^{-2} mmol) and L-DET 11.2 mg (4.54×10^{-2} mmol) in dry CH_2Cl_2 (10 ml) was stirred at −30 °C for 10 min. before adding (−)-**2** (10 mg, 4.54×10^{-2} mmol) and finally 5M TBHP (18.2 μl, 9.08×10^{-2} mmol). The homogeneous solution was stored in a freezer at −26 °C in a reaction vessel with a serum cap. The progress of the oxidation was monitored by TLC. After 14 h the flask was placed in a −30 °C bath and 10% aqueous tartaric acid (1.2 ml) was added to the solution with stirring. After 10 min the cooling bath was removed and stirring was continued at room temperature for 1 h, or until the aqueous layer became clear. The aqueous solution was extracted with CH_2Cl_2 (3× 30 ml). The combined organic extracts were washed with water (30 ml) and brine (3× 30 ml), dried over Na_2SO_4, and concentrated on a rotary evaporator to leave a colorless oil whose odor indicated contamination by TBHP. The oil was taken up in ether, in an ice bath, and stirred with 1 M NaOH (3 ml) at 0 °C for 30 min. The ether layer was washed with brine (3× 30 ml), dried over Na_2SO_4, and concentrated on a rotary evaporator to leave a clear oil. Chromatography on silica gel, eluting with a 4:1 mixture of hexane and AcOEt afforded (1*R*, 2*S*, 3*R*, 10*S*, 11*R*)-2,3-10,11-diepoxy-2,6,9,9-tetramethyl-6-cycloundecen-l-ol (−)-**4** (11 mg), mp 118.0–119.0 °C, $[\alpha]_D$ (23.5 °C) = −6.5 (EtOH, c = 1.01). IR (KBr) 3512, 2924, 1458 cm^{-1}; $^{1}HNMR$:δ 0.81 (s, 3H, CH_3 at C9), 1.13 (s, 3H, CH_3 at C9), 1.43 (s, 3H, CH_3 at C2), 1.43 (dddd, 1H, J = 3.63, 5.61, 6.26, and 9.57 Hz, H at C4), 1.67 (s, 3H, CH_3 at C6), 1.92 (d, 1H, J = 13.85 Hz, H at C8), 2.08 (ddd, J = 13.85, J = 3.63, 3.63, and 11.22 Hz, H at C5), 2.19 (ddd,

1H, $J = 3.63$, 6.26, and 7.60 Hz, H at C5), 2.24 (dd, 1H, $J = 9.90$ and 13.85 Hz, H at C8), 2.32 (dddd, 1H, $J = 5.28$, 5.61, 7.60, and 11.22 Hz, H at C4), 2.73 (d, 1H, $J = 2.31$ Hz, H at C10), 2.82 (dd, 1H, $J = 5.28$ and 9.57 Hz, H at C3), 2.99 (t, 1H, $J = 1.98$ Hz, H at C11), 4.18 (s, 1H, H at C1), 5.14 (d, 1H, $J = 9.90$ Hz, H at C7); ^{13}C δ NMR: 15.17 (CH_3 at C6), 15.33 (CH_3 at C2), 18.87 (CH_3 at C9), 23.99 (C4), 28.38 (CH_3 at C9), 33.64 (C9), 35.92 (C5), 38.73 (C8), 55.46 (C11), 56.21 (C3), 59.30 (C10), 59.95 (C2), 68.03 (C1), 122.73 (C7), 133.55 (C6). HRMS *m/z* calcd. mass for $C_{15}H_{24}O_3$ 252.1725, found 252.1728.

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