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Asymmetric synthesis of versatile monoepoxyzerumbone and monoepoxyzerumbol

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ABSTRACT

Versatile optically active 6,7-monoepoxyzerumbones (+)-**8** and (−)-**8** were obtained by oxidation of the corresponding monoepoxyzerumbols. Optically active erythro monoepoxyzerumbol (1*R*)-**9** and its acetate (1*S*)-**12**, and threo (1*R*)-**10** and its acetate (1*S*)-**11** were synthesized by lipase-catalyzed enantioselective transesterification of racemic compounds **9** and **10**. The absolute configuration of (1*R*)-**10** was determined by X-ray analysis after conversion to its ester with chlorine and that of (1*R*)-**9** was determined by conversion to the corresponding 6,7-monoepoxyzerumbone. Interestingly, the stereoselectivity of 6,7-monoepoxyzerumbol obtained by lipase-catalyzed transesterification contrasted with that of the 2,3,6,7,10,11-triepoxides.

1. Introduction

The chemistry of zerumbone plays a very important role in material sciences.[1–6] Zerumbone **1**[7] with its structural features has the potential to become one of the most important compounds displaying a NMRDOS[1] character and contains three double bonds: an isolated one at C6, and two at C2 and C10, which are part of a cross-conjugated dienone system. Of these, the C2 double bond appears the least hindered, with it being furthest from the *gem*-dimethyl substituents at C9.[8] Zerumbone **1** is a monocyclic sesquiterpene found as the major component of the essential oil of wild ginger, *Zingiber zerumbet* Smith. It is anticipated to be a powerful tool in the implementation of green chemistry with respect to the provision of materials produced from the cultivation of ginger. The largest amount of zerumbone is obtained when the rhizome is harvested in the summertime.[2]

Novel optically active substances as chiral building blocks derived from zerumbone[9–12] and containing three double bonds can be expected to be of use in various industrial fields such as medicine, perfumery, the liquid crystal industry, and the electronics industry.

We have already developed some optically active forms of zerumbone (Scheme 1). Chiral compounds **2** and **3** were prepared by Sharpless epoxidation,[9,10] while **4**, **5**, **6**, and **7** were prepared by lipase-catalyzed transesterification with high enantioselectivity.[11,12] Though it is possible to convert these derivatives into versatile materials, it is fair to say that the structure of zerumbone has not effectively been utilized. One of the reasons is that there is no conjugated carbonyl system in the structure of the above derivatives.

If optically active 6,7-monoepoxyzerumbols **9** and **10** are synthesized, optically active 6,7-epoxyzerumbones (+)-**8** and (−)-**8** with a conjugated system can be obtained by oxidation of the hydroxyl group. The optically active 6,7-monooxide of zerumbone can be expected to have applications as a chiral sources since we have already developed some useful reactions and structures using the racemic form.[3,6] Moreover, optically active 6,7-monoepoxyzerumbols **9** and **10** with simple structure might be also used as versatile chiral building block.

Herein, we report that a versatile chiral 6,7-monoepoxyzerumbone can be obtained by oxidation of the corresponding chiral 6,7-monoepoxyzerumbol readily prepared by lipase-catalyzed transesterification.

2. Results and discussion

As shown in Scheme 2, zerumbone **1** was treated with MCPBA at room temperature to afford racemic 6,7-epoxyzerumbone **8** in 90% yield.[6] Epoxide **8** was reacted with $LiAlH_4$ (LAH) in dry Et_2O at −10 °C for 80 min and the mixture of diastereoisomers was separated on silica gel chromatography to afford racemic erythro monoepoxyzerumbol **9** (*rac-e*-**9**) and the threo form **10** (*rac-t*-**10**) in 51% and 23% yields, respectively.

Monoclinic single crystals of *rac-t*-**10** was obtained by recrystallization from EtOH and subjected to a X-ray analysis. The X-ray structure showed the relative configuration to be (1*RS*,6*SR*,7*SR*) as shown in Figure 1.

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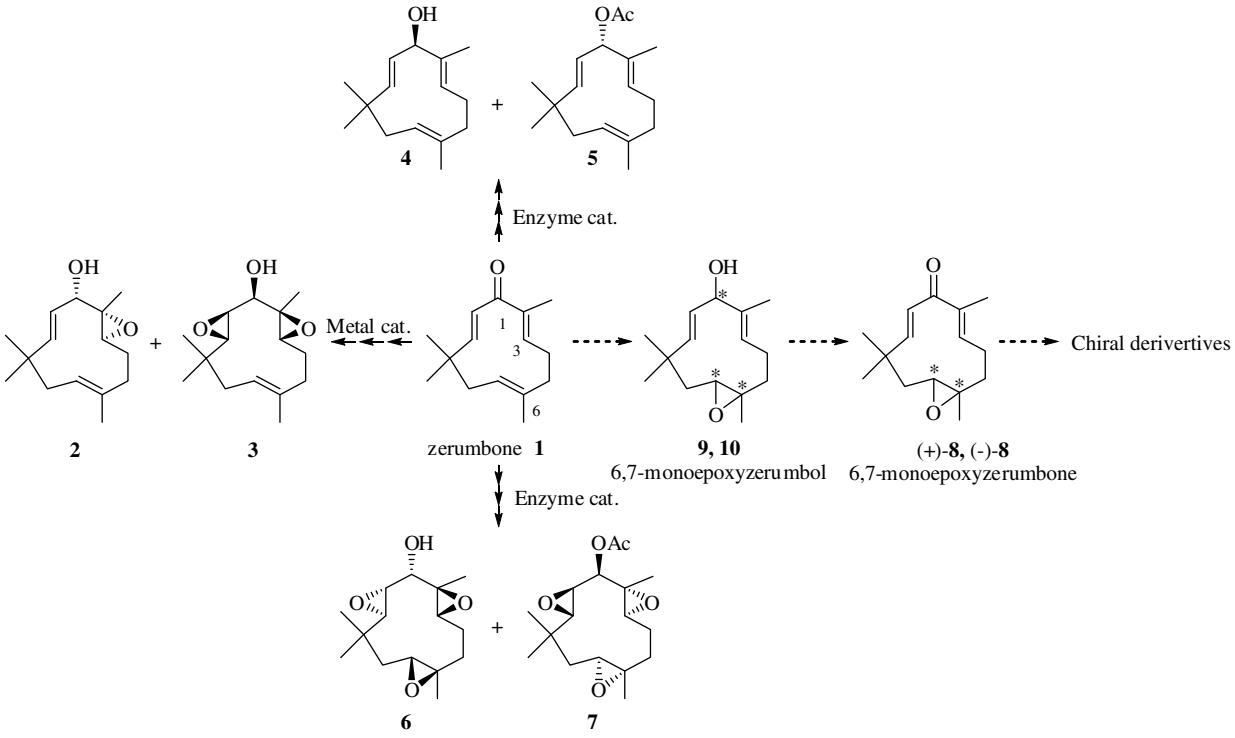
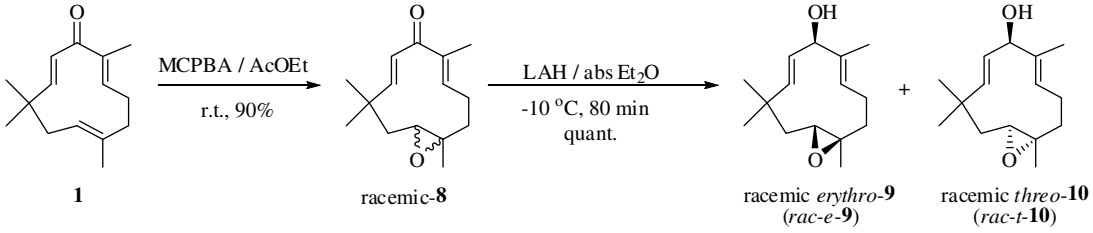


Scheme 1.



Scheme 2.

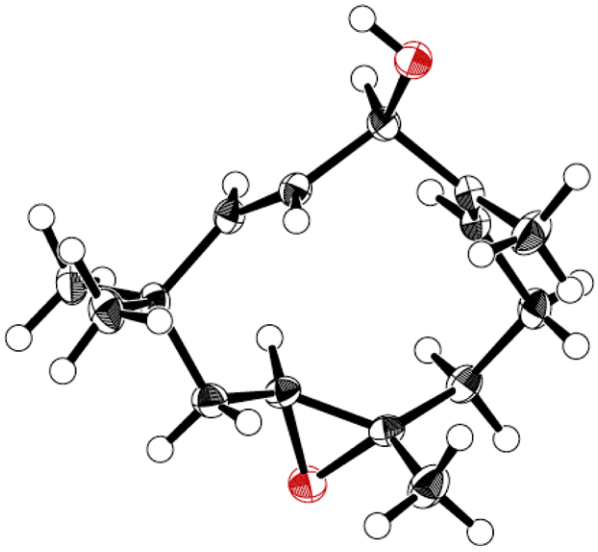
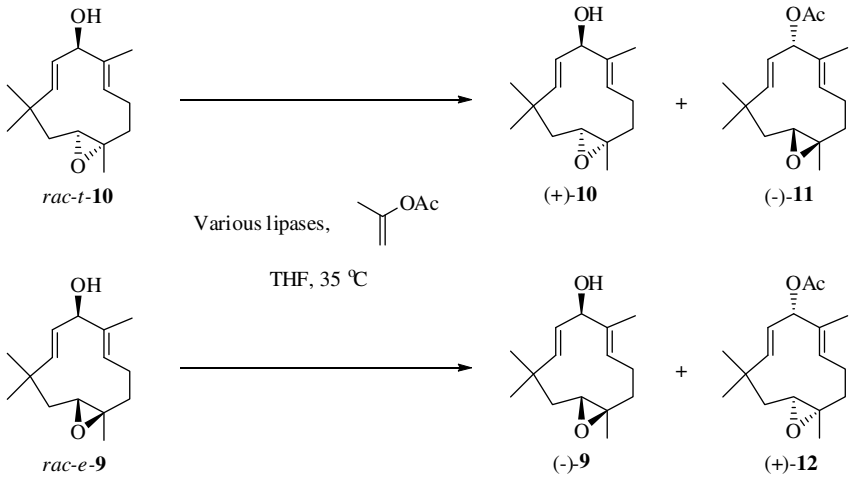


Figure 1. ORTEP drawing of the crystal structure of monozerumbol *rac-t*-**10**.

As shown in Scheme 3, the lipase-catalyzed kinetic transesterification of *rac-t*-**10** and *rac-e*-**9** was investigated. In many cases, either *n*-propyl ether, diisopropyl ether, or THF was recommended.[13] The reaction of *rac-t*-**10** was monitored by GC using a capillary column (DB-5), Inj: 200 °C, Det: 200 °C, column: 180 °C, column pressure: 80 kg/cm^2, retention time (**10**: 17 min, **11**: 22 min). The chirality was checked by GC using a capillary column (CP-CD; CP-cyclodextrin-B-236-M-19), Inj: 160 °C, Det: 160 °C, column: 140 °C, 160 kg/m^2, retention time ((−)-**10**: 66 min, (+)-**10**: 69 min, (+)-**11**: 67 min, (−)-**11**: 70 min). The reaction of *rac-e*-**9** was monitored by GC using a capillary column (DB-5, Inj: 200 °C, Det: 200 °C, column: 180 °C, column pressure: 80 kg/cm^2, retention time **9**: 15 min, **12**: 23 min). The chirality of acetyl derivative **12** was checked directly and another group **9** was checked, after oxidation of a hydroxyl group, by GC using a capillary column (CP-CD; CP-cyclodextrin-B-236-M-19), Inj: 230 °C, Det: 230 °C, column: 150 °C, 100kg/m^2, retention time ((−)-**8**: 63 min, (+)-**8**: 68 min, (+)-**12**: 66 min, (−)-**12**: 68 min).

Table 1 shows the results from the transesterification of *rac-t*-**10** with isopropenyl acetate in THF in the presence of 18 lipases. Several lipases, especially for *Alcaligenes* sp., produced the corresponding acetate in good yield.

The combination of Amano AK and THF gave the highest *E* value (enantiomeric ratio)[14] of 19; however, Meito QLM gave a good *E* value and reaction velocity to afford a large enantiomeric excess of optically active (+)-**10**.



Scheme 3.

Table 1
Transesterification of *rac-t*-**10** using various lipases in THF

Lipase	Source	Time (h)	Conversion (%)	*E* value
Meito AL	*Achromobacter* sp.	720	6.3	—
Meito PL	*Alcaligenes* sp.	720	14.9	—
Meito QL	*Alcaligenes* sp.	336	46.3	7
Meito QLM	*Alcaligenes* sp.	480	72.8	13
Amano A	*Aspergillus niger*	720	—	—
Amano PS	*Burkholderia cepacia*	720	8.0	—
Meito SL	*Burkholderia cepacia*	366	18.6	16
Meito MY	*Candida cylindracea*	720	0	—
Meito OF 360	*Candida cylindracea*	720	0	—
Amano AY	*Candida rugosa*	720	0	—
Amano M	*Mucorjavanicus*	720	0	—
Amano AK	*Pseudomonas stutzeri*	336	12.1	19
Amano GC	*Penicillium roqueforti*	720	0	—
Amano R	*Penicillium roqueforti*	720	0	—
Meito TL	*Pseudomonas stutzeri*	144	39.0	10
Meito UL	*Rhizopus* sp.	720	0	—
Pancreatin F	*Porcine liver*	720	0	—
PLE-A	*Porcine liver*	720	0	—

Plots of the rates of formation of (+)-**10** employing the lipases of Meito QLM in six solvents (DMF, DIPE, THF, EtOAc, toluene, and hexane) are shown in Figure 2. The reaction was slower in the polar solvent (DMF) and faster in the non-polar solvent (hexane). However, the enantioselectivity of both reactions was reduced in the transesterification. Consequently, the *E* value reached a maximum with the combination of the lipase and Meito QLM in a solvent of medium polarity, THF.

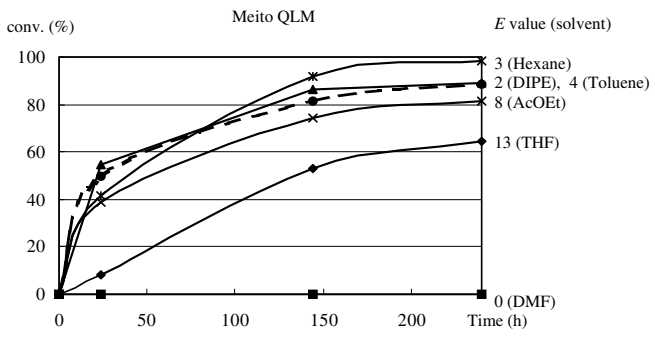


Figure 2. Reaction rate of transesterification of *rac-t*-**10**.

Table 2
Transesterification of *rac-t*-**10** at various temperatures

Temperature (°C)	Time (h)	Conversion (%)	*E* value
10	240	43	8
20–23	240	42	14
35	480	73	13
45	240	79	3
55	240	84	4

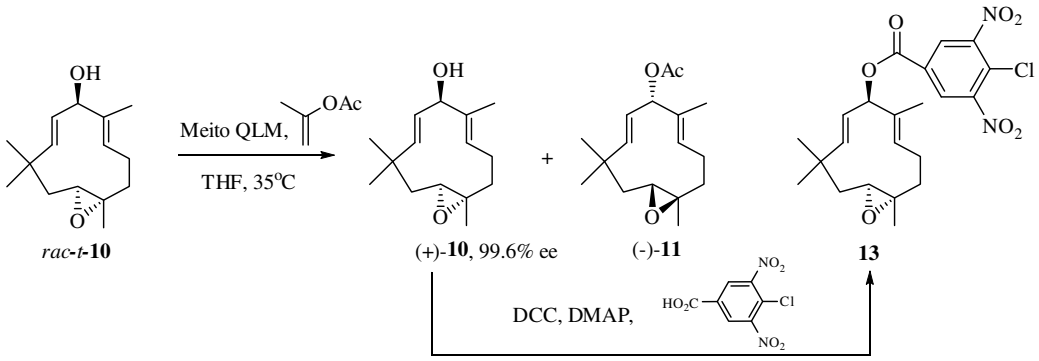
Table 2 shows the results from the transesterification of *rac-t*-**10** using Meito QLM with isopropenyl acetate in THF under various temperatures (10, 20–23, 35, 45, and 55 °C). Good enantioselectivities of transesterification with *rac-t*-**10** were observed between 20 and 35 °C.

As shown in Scheme 4, the absolute configuration of (+)-**10** was determined by anomalous dispersion of heavy atom derivatives. For this purpose, (+)-**10** was converted to its 4-chloro-3,5-dinitrobenzoate, **13**.

A monoclinic crystal of **13** was obtained by recrystallization from Et_2O, and subjected to X-ray analysis as shown in Figure 3. Consequently, it was determined that the absolute configuration of **13** was (1*R*,6*S*,7*S*). The Flack parameter[15] was 0.00.

Table 3 shows the results from the transesterification of *rac-e*-**9** with isopropenyl acetate in THF in the presence of 18 lipases. About half the number of lipases produced the corresponding acetate in good yield. The combination of Meito SL and THF gave the highest *E* value, 205; however, both Meito QLM and Meito TL gave a good *E* value and reaction velocity to afford a large enantiomeric excess of optically active (−)-**9**. Compared with *rac-t*-**10**, the transesterification reactivity and stereoselectivity of *rac-e*-**9** were very high. It was surprising that the difference in the epoxide position, away from the chiral carbon with a hydroxyl group, affected the reactivity of a lipase-catalyzed transesterification. Moreover, the transesterification of *rac-e*-**9** using Meito MY showed a contrary stereoselectivity compared with other lipases.

The stereoselectivity of *rac-e*-**9** using lipase-catalyzed transesterification was confirmed by the oxidation of the corresponding hydroxyl group. As shown in Scheme 5, (+)-(1*R*,6*S*,7*S*)-**10** with an already known absolute configuration was oxidized by the Dess–Martin reagent to obtain (6*S*,7*S*)-**8** in 78% yield. The sign of the specific rotation of (6*S*,7*S*)-**8** was negative. Meanwhile, the oxidation of (−)-**9** with Dess–Martin reagent gave (+)-(6*R*,7*R*)-**8** in 72% yield and the absolute configuration of (−)-**9** was determined as the (1*R*,6*R*,7*R*)-form.



Scheme 4.

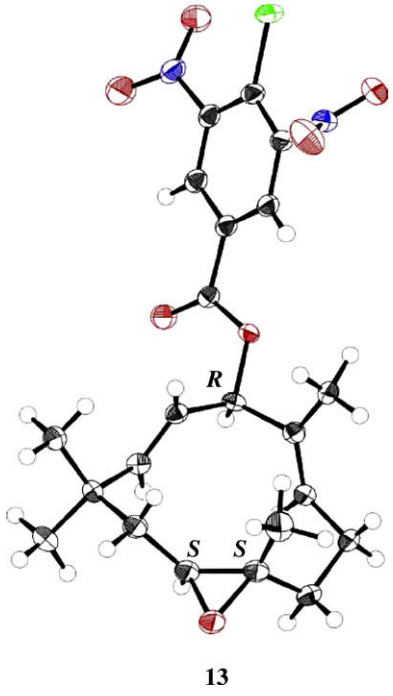


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Figure 3. ORTEP drawing of the crystal structures of **13**.

Table 3
Transesterification of *rac-e*-**9** using various lipases in THF

Lipase	Source	Time (h)	Conversion (%)	*E* value
Meito AL	*Achromobacter* sp.	670	12.5	85
Meito PL	*Alcaligenes* sp.	170	39.4	74
Meito QL	*Alcaligenes* sp.	170	51.9	26
Meito QLM	*Alcaligenes* sp.	70	53.8	22
Amano A	*Aspergillus niger*	670	0	—
Amano PS	*Burkholderia cepacia*	670	27.2	70
Meito SL	*Burkholderia cepacia*	170	54.0	205
Meito MY	*Candida cylindracea*	670	10.3	3
Meito OF 360	*Candida cylindracea*	670	5.5	—[a]
Amano AY	*Candida rugosa*	670	0	—
Amano M	*Mucorjavanicus*	670	0	—
Amano AK	*Pseudomonas stutzeri*	340	11.8	46
Amano GC	*Penicillium roqueforti*	670	0	—
Amano R	*Penicillium roqueforti*	670	0	—
Meito TL	*Pseudomonas stutzeri*	50	62.1	67
Meito UL	*Rhizopus* sp.	670	0	—
Pancreatin F	*Porcine liver*	670	0	—
PLE-A	*Porcine liver*	670	0	—

[a] Transesterification of *rac-e*-**9** using Meito MY showed contrary stereoselectivity compared with other lipases.

Surprisingly, the stereoselectivity of lipase-catalyzed transesterification of monoepoxides was in contrast to that of triepoxides. The stereoselectivity of the lipase appeared due to the recognition of hindrance in the vicinity of the chiral carbon, especially, the series of Meito QLM which has been investigated in terms of stereoselectivity.[16,17] As shown in Scheme 6, since the hindrance of the 2-methyl group of the monoepoxide could be recognized by the lipase, it acetylated *S* selectively. Meanwhile, the 9,9-*gem* methyl group of the triepoxide away from the chiral center, the hydroxyl group, might be recognized by the lipase since the efficiency of the hindrance of the 2-methyl group might be negated by the existence of both sides of the hydroxyl group with the epoxides.

3. Conclusion

The optically active compounds monoepoxyzerumbone (8*R*) and (8*S*) were obtained by oxidization from monoepoxyzerumbol, **9** or **10**, via lipase-catalyzed enantioselective transesterification of the racemic form. The absolute configurations of the optically active compounds were determined by single crystalline X-ray diffraction of their esters with chlorine using anomalous dispersion of heavy atom derivatives. We found that the lipase completely recognizes the difference in the epoxy position away from the chiral center, and the vicinal epoxy group of the chiral center affected the stereoselectivity of lipase-catalyzed transesterification.

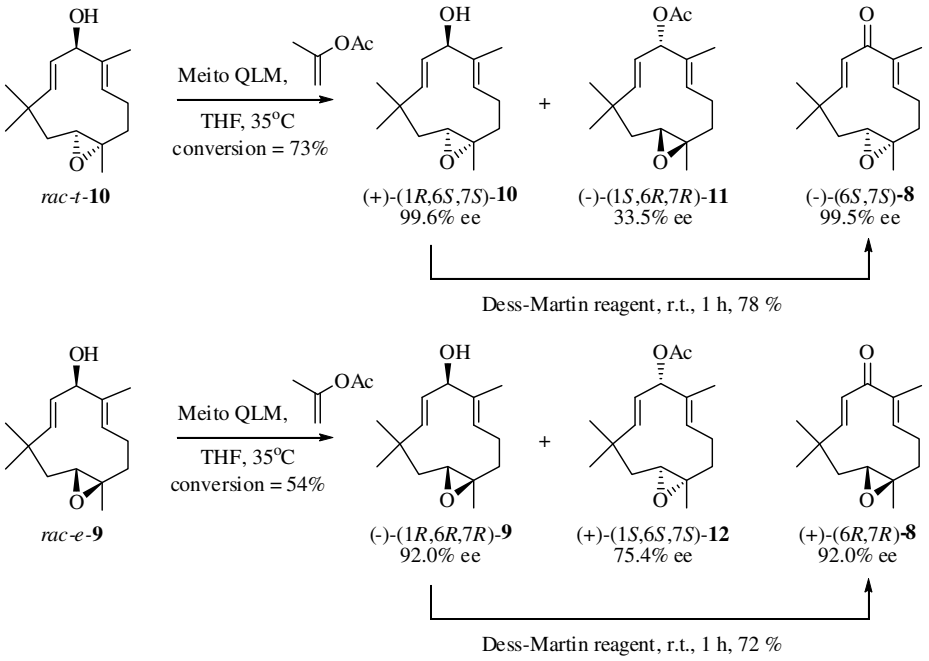
4. Experimental

4.1. General methods

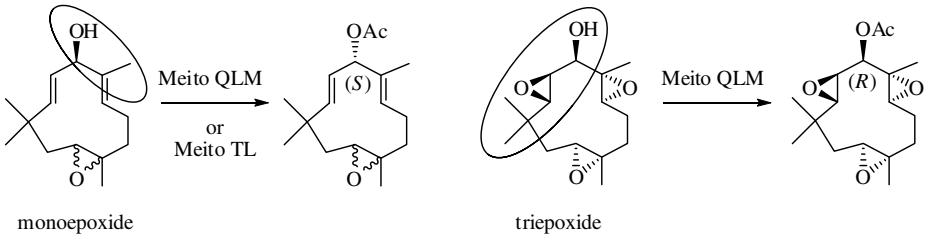
NMR spectra were obtained at 270 MHz for protons, and 68 MHz for ^{13}C in $CDCl_3$ with tetramethylsilane (TMS) as the internal standard, unless otherwise noted. Chemical shifts δ were reported in ppm from TMS. Mass spectra were recorded at 70 eV, and high-resolution mass spectra (HRMS) were obtained by direct injection. The X-ray diffraction and CCDC numbers appear in the section on compound data. Chemicals were of commercially available reagent grade, and used without further purification.

4.2. Reduction of 6,7-epoxyzerumbone 8

Under an atmosphere of N_2, 6,7-epoxyzerumbone **8** (3.0 g, 12.8 mmol) in absolute Et_2O (80 mL) was added dropwise to a suspension of $LiAlH_4$ (490 mg, 12.8 mmol) in absolute Et_2O (20 mL) at −10 °C, which was stirred for 80 min in an ice salt bath. The progress of the reaction was monitored by TLC (hexane/AcOEt = 4:1). Next H_2O (50 mL) and 2 M H_2SO_4 (10 mL) were added, after which Et_2O was removed by a rotary evaporator, and the mixture was ex-



Scheme 5.



Scheme 6.

tracted with EtOAc (3 × 30 mL). The combined organic solutions were washed with brine (3 × 30 mL), dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was subjected to silica gel column chromatography using $CHCl_3$ and Et_2O (30:1) as an eluent to afford (1*RS*,6*RS*,7*RS*)-erythro-6,7-epoxy-2,6,9,9-tetramethyl-2,10-cycloundecadien-1-ol, *rac-e*-**9** and afford (1*RS*,6*SR*,7*SR*)-threo-6,7-epoxy-2,6,9,9-tetramethyl-2,10-cycloundecadien-1-ol, *rac-t*-***10*** in 51% (1.5 g) and 23% (0.69 g) yields, respectively.

4.3. (1*RS*,6*RS*,7*RS*)-Erythro-6,7-epoxy-2,6,9,9-tetramethyl-2,10-cycloundecadien-1-ol, *rac-e*-9

Mp 100.5–101.5 °C. IR (KBr) 3277, 2958, 1296 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.05 (s, 3H, CH_3 at C9), 1.19 (s, 3H, CH_3 at C6), 1.19 (s, 3H, CH_3 at C9), 1.32–1.63 (ddd, 2H, J = 14.2, 9.9 and 9.9 Hz, CH_2 at C8), 1.72 (s, 3H, CH_3 at C2), 2.02–2.06 (m, 1H, CH at C5), 2.08–2.15 (m, 1H, CH at C4), 2.25–2.30 (m, 1H, CH at C4), 2.48 (d, 1H, J = 9.9 Hz, CH at C7), 4.72 (d, 1H, J = 6.9 Hz, CH at C1), 5.38 (d, 1H, J = 15.8 Hz, CH at C10), 5.48 (dd, 1H, J = 9.9 and 8.3 Hz, CH at C3), 5.75 (dd, 1H, J = 16.2 and 6.9 Hz, CH at C11), ^{13}C NMR δ 12.9 (CH_3 at C6), 16.1 (CH_3 at C9), 22.6 (C4), 22.9 (CH_3 at C9), 30.5 (CH_3 at C6), 35.0 (C9), 37.8 (C5), 40.3 (C8), 61.4 (C6), 63.4 (C7), 78.0 (C1), 124.8 (C3), 132.0 (C11), 139.3 (C10), 143.1 (C2). HRMS: *m/z* calcd mass for $C_{15}H_{24}O_2$ 236.1776, found 236.1773.

4.4. (1*RS*,6*SR*,7*SR*)-Threo-6,7-epoxy-2,6,9,9-tetramethyl-2,10-cycloundecadien-1-ol, *rac-t*-10

Mp 99.0–99.5 °C. IR(KBr) 3461, 2956, 1447 cm^{-1}. ^1H NMR: δ 1.08 (s, 3H, CH_3, at C9), 1.12–1.16 (m, 1H, CH at C5), 1.18 (s, 3H, CH_3 at C9), 1.19 (s, 3H, CH_3 at C6), 1.41–1.63 (dd, 2H, J = 14.2 and 8.9 Hz, 2H at C8), 1.72 (s, 3H, CH_3 at C2), 2.06–2.13 (m, 1H at C5), 2.16–2.24 (m, 2H, H at C4), 2.52 (d, 1H, J = 8.9 Hz, H at C7), 4.66 (s, 1H, H at C1), 5.43 (t, 1H, J = 7.9 Hz H at C3), 5.80 (d, 1H, J = 1.3 Hz, H at C11), 5.81 (s, 1H, H at C10), $^{13}CNMR$: δ 13.7 (CH_3 at C2), 16.4 (CH_3 at C9), 23.0 (C4), 25.5 (CH_3 at C6), 29.5 (CH_3 at C9), 34.2 (C9), 38.3 (C5), 42.1 (C8), 61.3 (C6), 62.8 (C7), 75.8 (C1), 124.3 (C3), 132.1 (C11), 138.6 (C10), 141.0 (C2). HRMS: *m/z* calcd mass for $C_{15}H_{24}O_2$ 236.1776, found 236.1763.

4.5. Crystallographic study of *rac-t*-10

A colorless prism, 0.50 × 0.40 × 0.30 mm, primitive, space group $P2_1/n$ (no. 14), a = 10.831(3), b = 16.132(4), c = 16.268(5) Å, β = 98.334(12)°, V = 2812.5(13) $Å^3$, Z = 8, D_c = 1.116 g/cm^3, μ(Mo Kα) = 0.717 cm^{-1}, was used for data collection. The intensity data were measured on a Rigaku Mercury CCD detector using Mo Kα radiation at a temperature of −180 + 1 °C. The structure was solved by direct methods (SIR97)[18] and expanded using Fourier techniques (DIRDIF99).[19] All the calculations were performed using the CRYSTAL-

STRUCTURE crystallographic software package. The final cycle of full-matrix least-squares refinement was based on 6408 observed reflections ($I > 2.00\sigma(I)$) and 500 variable parameters and gave $R_1 = 0.0487$ and $wR_2 = 0.1479$. The value of the goodness of fit indicator was 1.011. (Summary of Data CCDC 688470.)

4.6. General procedure of lipase-catalyzed transesterification of *rac-t*-10

A mixture of *rac-t*-**10** (1.0 g, 4.23 mmol), isopropenyl acetate (2.0 mL, 500 mmol), and the lipase (dry Meito QLM, 1.00 g) in THF (50 mL: water content <1.0% v/v) was stirred for 480 h at 35 °C. The conversion was 72.8%. The reaction was followed by gas chromatography using a column of DB-5 (detector and injection temperature, 200 °C; column temperature, 180 °C; carrier gas, He; FID detector). Under these conditions, the retention time of *rac-t*-**10** and its corresponding acetate were 17 min and 22 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 EtOAc, afforded (+)-**10** and (−)-acetate **11** in 99.6% and 33.5% ees, respectively, as determined by gas chromatography using a column of CPCD (detector and injection temperature, 160 °C; column temperature, 140 °C; carrier gas He; FID detector). Under these conditions, the retention times of (−)-**10**, (+)-**10**, (+)-**11**, and (−)-**11** were 66, 69, 67, and 70 min, respectively.

4.7. (1*R*,6*S*,7*S*)-6,7-Epoxy-2,6,9,9-tetramethyl-2,10-cycloundecadien-1-ol, (+)-10

Mp 94.0–96.5 °C. $[\alpha]_D^{23.5} = +82.4$ (*c* 1.00, $CHCl_3$), 99.6% ee.

4.8. (1*S*,6*R*,7*R*)-1-Acetoxy-6,7-epoxy-2,6,9,9-tetramethyl-2,10-cycloundecadiene, (−)-11

Colorless oil. $[\alpha]_D^{23.5} = -31.4$ (*c* 1.02, $CHCl_3$), 33.5% ee. IR (NaCl film) 2960, 1745, 1450 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.08 (s, 3H, CH_3 at C9), 1.06–1.28 (m, 1H, H at C5), 1.17 (s, 3H, CH_3 at C9), 1.21 (s, 3H, CH_3 at C6), 1.35–1.67 (d, 2H, *J* = 8.9 Hz, CH at C8), 1.70 (s, 3H, CH_3 at C2), 2.04–2.18 (m, 1H, CH at C5), 2.10 (s, 3H, CH_3 at CH_3CO), 2.20–2.34 (m, 2H, CH at C4), 2.57 (d, 1H, *J* = 8.9 Hz, CH at C7), 5.35 (t, 1H, *J* = 7.6 Hz, CH at C3), 5.52 (s, 1H, CH at C1), 5.79 (d, 1H, *J* = 1.3 Hz, CH at C11), 5.80 (s, 1H, CH at C10), ^{13}C NMR δ 13.5 (CH_3 at C2), 16.4 (CH_3 at C9), 21.1 (CH_3CO), 23.4 (C4), 25.7 (CH_3 at C6), 29.2 (CH_3 at C9), 34.4 (C9), 38.3 (C5), 42.5 (C8), 61.3 (C6), 62.6 (C7), 77.3 (C1), 126.7 (C3), 128.4 (C11), 137.5 (C10), 141.2 (C2), 170.2 (CO). HRMS: *m/z* calcd mass for $C_{17}H_{26}O_3$ 278.1882, found 278.1877.

The procedure for lipase-catalyzed transesterification of *rac-e*-**9** followed the same method as mentioned above.

4.9. (1*R*,6*R*,7*R*)-6,7-Epoxy-2,6,9,9-tetramethyl-2,10-cycloundecadien-1-ol, (−)-9

Mp 129.5–131.0 °C. $[\alpha]_D^{23.5} = -43.1$ (*c* 1.01, $CHCl_3$), 92.0% ee.

4.10. (1*S*,6*S*,7*S*)-1-Acetoxy-6,7-epoxy-2,6,9,9-tetramethyl-2,10-cycloundecadiene, (+)-12

$[\alpha]_D^{23.5} = +5.1$ (*c* 1.01, $CHCl_3$), 86.9% ee. IR(KBr) 2962, 1730, 1448 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.06 (s, 3H, CH_3 at C9), 1.13–1.29 (m, 1H, H at C5), 1.20 (s, 3H, CH_3 at C9), 1.20 (s, 3H, CH_3 at C6), 1.35–1.67 (dd, 2H, *J* = 14.2 and 9.9 Hz, CH at C8), 1.70 (s, 3H, CH_3 at C2), 1.85–2.09 (m, 1H, CH at C5), 2.09 (s, 3H, CH_3 at CH_3CO), 2.21–2.32 (m, 2H, CH at C4), 2.57 (d, 1H, *J* = 9.6 Hz, CH at C7), 5.44 (d, 1H, *J* = 16.2 Hz, CH at C10), 5.54 (dd, 1H, CH at C3), 5.55 (d, 1H, *J* = 6.9 Hz, CH at C1), 5.72 (dd, 1H, *J* = 16.2 and 6.6 Hz CH at C11), ^{13}C NMR δ 13.7 (CH_3 at C2), 16.1 (CH_3 at C9), 21.1 (CH_3CO), 22.9 (C4), 22.9 (CH_3 at C6), 30.4 (CH_3 at C9), 35.3 (C9), 38.0 (C5), 40.4 (C8), 61.3 (C6), 63.2 (C7), 79.1 (C1), 127.4 (C3), 128.5 (C11), 140.4 (C2), 140.8 (C10), 170.4 (CO). HRMS: *m/z* calcd mass for $C_{17}H_{26}O_3$ 278.1882, found 278.1872.

4.11. Crystallographic study of (+)-10

A colorless prism crystal, crystal size 0.60 × 0.40 × 0.20 mm^3, orthorhombic, space group $P2_12_12_1$ (no. 19), $a = 8.977(5)$, $b = 9.823(4)$, $c = 15.604(10)$ Å, $V = 1375.9(13)$ Å^3, $Z = 4$, $D_{calcd} = 1.141$ g/cm^3, μ(Mo Kα) = 0.733 cm^{-1}, was used for data collection. The intensity data were measured on a Rigaku R-AXIS RAPID using Mo Kα radiation at a temperature of −180 ± 1 °C. The structure was solved by direct methods (SIR97)[18] and expanded using Fourier techniques (DIRDIF99).[19] All calculations were performed using the CRYSTALSTRUCTURE crystallographic software package. The final cycle of full-matrix least-squares refinement on F^2 was based on 12,775 reflections (all data) and 3121 variable parameters and gave $R_1 = 0.035$ ($I > 2.0\sigma(I)$) and $wR_2 = 0.062$ (all data). The value of the goodness of fit indicator was 1.046. Flack parameter was −0.3 (1).[15] (Summary of Data CCDC 688471.)

4.12. (1*R*,6*S*,7*S*)-6,7-Epoxy-2,6,9,9-tetramethylcycloundeca-2,10-dienyl 4-chloro-3,5-dinitrobenzoate 13

Under an atmosphere of N_2, a mixture of (+)-**10** (30.7 mg, 0.13 mmol), 4-dimethylaminopyridine (3.8 mg, 0.03 mmol), 4-chloro-3,5-dinitrobenzoic acid (33.2 mg, 0.14 mmol), and *N,N′*-dicyclohexylcarbodiimide (39.1 mg, 0.19 mmol) in 3 mL anhydrous CH_2Cl_2 was stirred at 0 °C for 5 min and then at room temperature for 3 h. Water (20 mL) was the added to the solution and the reaction mixture stirred for 20 min. The precipitated urea was filtered off and the filtrate extracted with CH_2Cl_2 (2 × 20 mL). The combined organic solutions were washed with 0.5 M HCl and saturated aq $NaHCO_3$, and then dried over Na_2SO_4, and concentrated on a rotary evaporator to afford a light yellow solid residue. Chromatography on silica gel, eluting with a 4:1 mixture of hexane and EtOAc, afforded **13** in 6.8% yield. ^1H NMR ($CDCl_3$): δ 1.10 (s, 3H, CH_3 at C9), 1.14–1.22 (m, 1H, H at C5), 1.19 (s, 3H, CH_3 at C6), 1.25 (s, 3H, CH_3 at C9), 1.50 (dd, 2H, *J* = 9.5 and 14.2 Hz, CH at C8), 1.69 (d, 2H, *J* = 14.2 Hz, CH at C8), 1.78 (s, 3H, CH_3 at C2), 2.13–2.20 (m, 1H, CH at C5), 2.22–2.35 (m, 1H, CH at C4), 2.60 (d, 1H, *J* = 9.1 Hz, CH at C7), 5.39–5.45 (m, 1H, CH at C3), 5.84 (s, 1H, CH at C1), 5.92 (d, 1H, *J* = 3.0 Hz, CH at C11), 5.92 (s, 1H, CH at C10), 8.58 (s, 2H, CH at C2′). ^{13}C NMR δ 13.7 (CH_3 at C2), 16.6 (CH_3 at C6), 23.7 (C5), 26.1 (CH_3 at C9), 29.2 (CH_3 at C9), 34.7 (C9), 38.4 (C4), 42.9 (C8), 61.2 (C6), 62.4 (C7), 80.2 (C1), 124.5 (C1'), 127.5 (C11), 127.9 (C2′) 128.4 (C3), 131.0 (C4′), 135.9 (C2), 143.2 (C10), 149.5 (C3′), 160.9 (CO). Elemental Anal. Calcd for $C_{22}H_{25}ClN_2O_7$: C, 56.84; H, 5.42; N, 6.03. Found: C, 56.54; H, 5.69; N, 5.83.

4.13. Crystallographic study of 13

A colorless prism crystal, crystal size 0.40 × 0.30 × 0.04 mm^3, monoclinic, space group $P2_1$ (no. 4), $a = 8.412(3)$, $b = 11.157(6)$, $c = 12.221(3)$ Å, $\beta = 103.647(13)°$, $V = 1114.6(8)$ Å^3, $Z = 2$, $D_{calcd} = 1.385$ g/cm^3, μ(Mo Kα) = 2.174 cm^{-1}, was used for data collection. The intensity data were measured on a Rigaku R-AXIS RAPID using Mo Kα radiation at a temperature of −180 ± 1 °C. The structure was solved by direct methods (SIR97)[18] and expanded using Fourier techniques (DIRDIF99).[19] All calculations were performed using the CRYSTALSTRUCTURE crystallographic software package. The final cycle of full-matrix least-squares refinement on F^2 was based on 10,898 reflections (all data) and 4990 variable parameters and gave $R_1 = 0.030$ ($I > 2.0\sigma(I)$) and $wR_2 = 0.084$ (all data). The value of the

goodness of fit indicator was 1.006. The Flack parameter was −0.00 (4).[15] (Summary of Data CCDC 688472.)

4.14. (6*S*,7*S*)-6,7-Epoxy-2,6,9,9-tetramethyl-2,10-cycloundecadien-1-one, (−)-8

Under an N_2 atmosphere, Dess–Martin periodinane (92.7 mg, 0.22 mmol) was added into CH_2Cl_2 (3 mL) at room temperature and stirred until the mixture was completely dissolved. Compound (+)-**10**, 51 mg (0.22 mmol), in CH_2Cl_2 (1.5 mL) was dropped into the Dess–Martin solution and then stirred at the same temperature for 1 h. The progress of the reaction was monitored by TLC (hexane/AcOEt = 4:1). Next, CH_2Cl_2 (30 mL) and 1 M NaOH aq (30 mL) were added into the solution, and then the aqueous solution was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with brine (3 × 30 mL), dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was subjected to silica gel column chromatography using hexane and AcOEt (4:1) as an eluent to afford (6*S*,7*S*)-2,3-epoxy-2,6,9,9-tetramethyl-2,10-cycloundecadien-1-one, (−)-**8** in 78% yield.

$[\alpha]_D^{23.5} = -9.7$ (*c* 1.000, $CHCl_3$), 99.5% ee. Mp 119.0–122.0 °C (racemic 96.0–96.5 °C).[6] IR (KBr) cm^{-1}: 1657, 1263. ^1H NMR: δ 1.10 (s, 3H, CH_3 at C9), 1.22 (s, 3H, CH_3 at C6), 1.31 (s, 3H, CH_3 at C9), 1.27–1.36 (m, 1H, H at C5), 1.45 (dd, 1H, J = 11.3 and 14.0 Hz, CH at C8), 1.85 (s, 3H, CH_3 at C2), 1.93 (d, 1H, J = 14.0 Hz, CH at C8), 2.26–2.43 (m, 3H, CH_2 at C4 and CH at C5), 2.72 (dd, 1H, J = 1.4 and 11.3 Hz, H at C7), 6.07–6.12 (m, 3H, 3H at C2, C10 and C11); ^{13}C NMR δ 12.3 (CH_3 at C2), 15.8 (CH_3 at C6), 23.9 (CH_3 at C9), 24.8 (C4), 30.0 (CH_3 at C9), 36.1 (C9), 38.2 (C5), 42.8 (C8), 61.2 (C6), 62.8 (C7), 128.6 (C11), 139.3 (C2), 147.6 (C3), 159.3 (C10), 202.3 (C1). Elemental Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.96; H, 9.41.

4.15. (6*R*,7*R*)-6,7-Epoxy-2,6,9,9-tetramethyl-2,10-cycloundecadien-1-one, (+)-8

(+)-**8** was prepared from (−)-**9**. $[\alpha]_D^{23.5} = +7.8$ (*c* 1.000, $CHCl_3$), 92.0% ee.

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