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Total Synthesis of (S)-(+)-Curcudiol, (S)- and (R)-(-)-Curcuphenol Based on Enzymatic Resolution of a Primary Alcohol Possessing One Stereogenic Center

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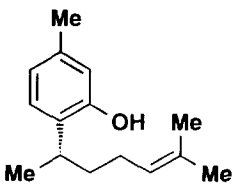
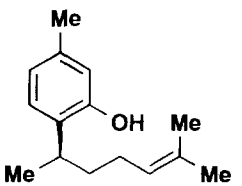
Abstract: A highly stereoselective synthesis of the versatile chiral synthons possessing one stereogenic center, (S)-**3** and (R)-**3** was achieved and the application of (S)-**3** and (R)-**3** into the total syntheses of (S)-curcuphenol (**1**), (S)-curcudiol (**2**) and (R)-curcuphenol (**1**), respectively, was described.

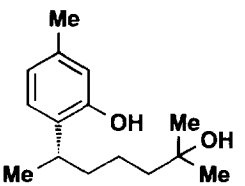
Although numerous syntheses of racemic bisabolane sesquiterpenes have been known,[1] the useful asymmetric syntheses have not been reported so far except for the synthesis of (R)-(-)-curcuphenol (**1**) from (R)-(+)-citronellal.[2] Among them, (S)-(+)-curcuphenol (**1**), isolated from a marine sponge *Epipolasis* sp. inhibits strongly the activity of gastric H, K-ATPase,[3] while (R)-(-)-curcuphenol (**1**), isolated from a Caribbean gorgonian *Pseudopterogorgia rigida* and *Lasianthaea podocephala* exhabits antibacterial activities against *Staphylococcus aureus* and *Vibrio anguillarum*.[4] We now report that (S)-**1**, (R)-**1**, and (S)-curcudiol (**2**) have been synthesised based on enzymatic resolution using immobilized lipase in organic solvent.



(S)-1

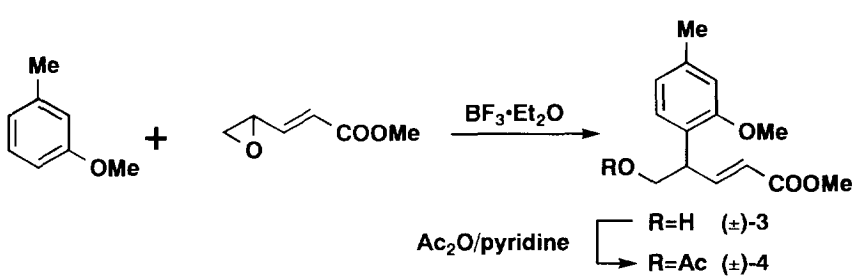


(R)-1



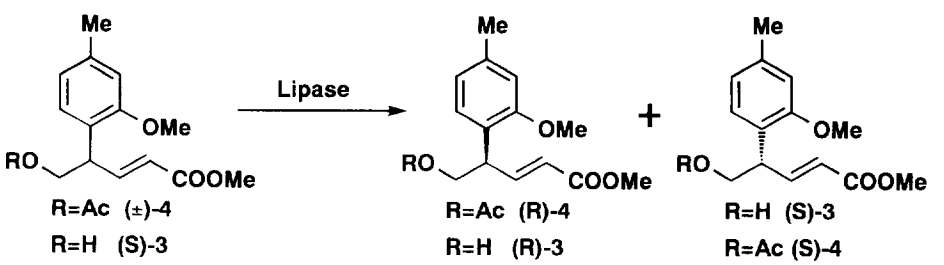
(S)-2

The most intriguing point of the present synthesis is the preparation of the optically active primary alcohols possessing one stereogenic center eq. (S)- and (R)-**3**. This was successfully achieved by carrying out an enantioselective hydrolysis of (±)-acetate **4** obtained by the acetylation of (±)-**3**, using immobilized lipase. The desired racemic (±)-**3** was already obtained in the reaction of methyl (4,5)-epoxy-(2*E*)-pentenoate and *m*-methoxytoluene in the presence of $BF_3.Et_2O$ by us.[5]



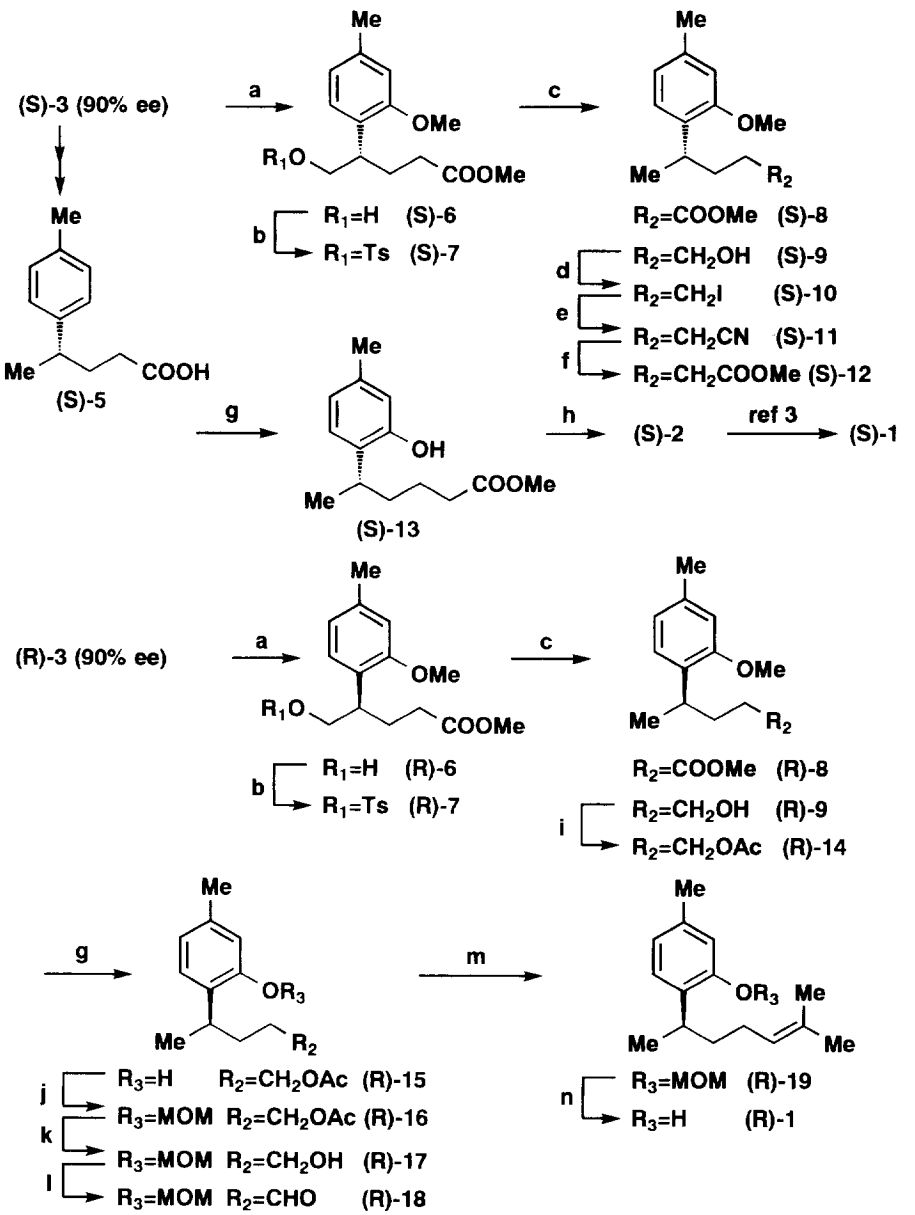
Initially, (±)-**4** was subjected to screening experiments using several kinds of commercially available lipases. Among them, two lipases "MY-30" from *Candida cylindracea* and "OF-360" from *Candida cylindracea* were found to be effective. When (±)-**4** was subjected to the enantioselective hydrolysis using "MY-30" in water saturated isopropyl ether, an alcohol (S)-**3** (27%, 80% ee)[6] and the unchanged (R)-**4** (69%, 36% ee) were obtained. On the other hand, asymmetric hydrolysis of (±)-**4** using "OF-360" gave (S)-**3** (60%, 51% ee) and (R)-**4** (38%, 83% ee). The desired stereochemistry of **3** was found to be governed by the selection of lipase. Then immobilized lipases "MY-30" and "OF-360" were obtained by illumination of a mixture consisting of a photo-crosslinkable resin prepolymer ENTP-4000,[7] a photo-sensitizer such as benzoin ethyl ether and the crude lipases "MY-30" and "OF-360", respectively. Using the immobilized lipases afforded the much better results as shown in table [entry 2, (S)-**3**, 85% ee; entry 4, (R)-**4**, 90% ee]. The alcohol (S)-**3** having 80% enantiomeric excess was subjected to the enantioselective acetylation using "OF-360" in the presence of isopropenyl acetate in isopropyl ether to afford (S)-**4** (74%, 90% ee, $[\alpha]_D$ -7.2, c=0.46, MeOH) and (R)-**3** (16%, 30% ee). Treatment of (S)-**4** and (R)-**4** (entry 4, 90% ee) with MeONa in MeOH produced (S)-**3** (90% ee, $[\alpha]_D$ -15.1, c=0.67, MeOH) and (R)-**3** (90% ee), respectively. The enantiomerie purity of the obtained chiral compounds was determined by HPLC on a CHIRALCEL OD (250 X 4.6 mm) column. In order to confirm the absolute configuration of the present (-)-**3**, (-)-**3** was successfully converted to the reported acid (S)-**5**.[8] Thus the absolute structure of (-)-**3** was determined to be S. Then total synthses of (S)-curcudiol **2**, (R)-curcuphenol (**1**) and (S)-**1** formally derived from (S)-**2**,[3] were achieved from (S)-**3** (90% ee) and (R)-**3** (90% ee), respectively. Catalytic hydrogenation of (S)-**3** gave (S)-**6** followed by treatment of tosyl chloride to afford (S)-**7** [83% overall yield from (S)-**3**]. $NaBH_4$ reduction of (S)-**7** provided (S)-**8** (42%) and (S)-**9** (40%). Conversion of (S)-**9** into the one-carbon homologation product (S)-**11** was achieved by the standard procedure [iodination, (S)-**10**

Table



Entry	Substrate(g)	Lipase	Products %(% ee)	%(% ee)
1	(±)-4 (0.2)	MY-30 (*Candida cylindracea*)	(R)-4 69(36)	(S)-3 27(80)
2	(±)-4 (0.25)	Immobilized lipase (MY-30)	(R)-4 77(24)	(S)-3 22(85)
3	(±)-4 (0.2)	OF-360 (*Candida cylindracea*)	(R)-4 38(83)	(S)-3 60(51)
4	(±)-4 (0.2)	Immobilized lipase (OF-360)	(R)-4 40(90)	(S)-3 52(58)
5*	(S)-3 (0.1)	OF-360	(S)-4 74(90)	(R)-3 16(30)

* Optically active (S)-3 (80% ee) was employed.



a; $H_2/Pd(OH)_2$-C b; TsCl/pyridine c; $NaBH_4$/DMSO d; I_2/PPh_3

e; NaCN/DMF f; 1) NaOH/EtOH 2) CH_2N_2 g; EtSH/$AlCl_3$ h; MeMgI/Et_2O

i; Ac_2O/pyridine j; $MeOCH_2Cl$/NaH/18-Crown-6 k; 1N-NaOH/MeOH

l; PCC/CH_2Cl_2 m; Ph_3P^+-$CHMe_2$ I^-/n-BuLi n; 2N-HCl/*i*-PrOH

(48%), CN-substitution, (S)-**11** (99%)]. An alkaline hydrolysis of (S)-**11** followed by the successive esterification gave the methyl ester (S)-**12** (54% overall yield from (S)-**11**, $[\alpha]_D$ +6.2, c=1.15, MeOH). Demethylation of (S)-**12** with a combination of $AlCl_3$ and EtSH provided a phenol (S)-**13**, which was treated with Grignard reagent to afford (S)-curcudiol (**2**) ($[\alpha]_D$ +9.9, c=4.96, $CHCl_3$; corresponds to 90% ee) in 91 % overall yield from (S)-**12**. The spectral data ($[\alpha]_D$, ^{1}H-NMR and ^{13}C-NMR) of the synthesized (S)-**2** were identical with those ($[\alpha]_D$ +9.2, c=10.8, $CHCl_3$)[3b] of natural (S)-**2**, which is converted into (S)-curcuphenol (**1**) in the literature.[3] The synthesis of (R)-curcuphenol (**1**) from (R)-**3** (90% ee) was carried out foundamentally by the same way as that of (S)-**3**. Conversion of (R)-**3** into the alcohol (R)-**9** was achieved by the same route [(R)-**7**, 83% overall yield from (R)-**3**, (R)-**8** (47%) and (R)-**9** (26%)] as the previous case. Acetylation [(R)-**14**, 90%] of (R)-**9** followed by demethylation provided the phenol (R)-**15** (97%), which was treated with methoxymethyl chloride (MOMCl) to give the MOM ether (R)-**16** in 97% yield. Hydrolysis [(R)-**17**, 98%] of (R)-**16** followed by oxidation provided the aldehyde [(R)-**18**], which was subjected to the Wittig reaction to afford (R)-**19** [62% overall yield from (R)-**17**)]. Deprotection of (R)-**19** gave (R)-curcuphenol (**1**) (62% yield, $[\alpha]_D$ -20.9, c=1.73, $CHCl_3$; corresponds to 90% ee), whose spectral data ($[\alpha]_D$, ^{1}H-NMR and ^{13}C-NMR) were identical with those ($[\alpha]_D$ -23.6 , $CHCl_3$) [2] of natural product (R)-**1**.

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A detailed conversion procedure will be reported in the forthcoming paper.

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