Total Synthesis of (S)-(−)-Curcudiol, and (S)-(+)− and (R)-(−)-Curcuphenol

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A highly enantioselective synthesis of the versatile chiral synths possessing one stereogenic center, (S)- and (R)-4-aryl-5-hydroxy-(2E)-pentenoate (3) was achieved based on the enzymatic reaction of (±)-3 with commercially available lipases MY-30 or OF-360 from Candida rugosa. Application of (S)-3 and (R)-3 to the total syntheses of (S)-curcudiol (1), (S)-curcudiol (2), and (R)-curcuphenol (1), respectively, is described.

Key words bisabolane sesquiterpene; enantioselective hydrolysis; lipase; total synthesis

The phenolic sesquiterpenes of the bisabolane family have been isolated from many different natural sources. Among them, (S)-(−)-curcudiol (1), isolated from the marine sponge Epipolasis sp. strongly inhibits the activity of gastric H, K-ATPase, while (R)-(−)-curcuphenol (1), isolated from the Caribbean gorgonians Pseudopterogorgia rigida and Lasianthaea podocephala, exhibits antibacterial activities against Staphylococcus aureus and Vibrio anguillarum. Accordingly, the establishment of an efficient and general synthetic route to both enantiomers of these sesquiterpenoids is of significance. Although racemic syntheses of bisabolane sesquiterpenes have been developed, useful asymmetric synthesis bearing a benzylic asymmetric center have not been reported except for a few examples.

We now report that (S)-1, (R)-1, and (S)-curcudiol (2) have been synthesized based on enzymatic resolution using immobilized lipase in organic solvent.

The most intriguing point of the present synthesis is the preparation of the optically active primary alcohols possessing one stereogenic center of (S)- and (R)-4-aryl-5-hydroxy-(2E)-pentenoate (3). This was successfully achieved by carrying out enantioselective hydrolysis of the reported (±)-acetate 4 using immobilized lipase. The desired racemic (±)-3 had previously been obtained by us in the reaction of methyl (4,5)-epoxy-(2E)-pentenoate and m-methoxytoluene in the presence of BF₃·Et₂O.

Initially, (±)-4 was subjected to screening experiments using several types of commercially available lipases. Among them, the two lipases MY-30 and OF-360 from Candida rugosa were found to be effective. When (±)-4 was subjected to enantioselective hydrolysis using MY-30 in water-saturated isopropyl ether, the alcohol (S)-3 (27%, 80% ee) and 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 the photo-crosslinkable resin prepolymer ENTP-4000, a photosensitizer such as benzoin ethyl ether and the crude lipases MY-30 and OF-360, respectively. Using the immobilized lipases afforded much better results, as shown in Table 1 [entry 2, (S)-3, 85% ee; entry 4, (R)-4, 90% ee]. The alcohol (S)-3 with 80% enantiomeric excess was subjected to enantioselective acetylation using OF-360 in the presence of isopropenyl acetate in isopropyl ether to afford (S)-4 [74%, 90% ee, [α]D −7.2° (c=0.46, MeOH)] and (R)-3 (16%, 30% ee).

Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate Lipase</th>
<th>Products (%)</th>
<th>Products (% ee)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(±)-4 (1) MY-30</td>
<td>(R)-4 69 (36)</td>
<td>(S)-3 27 (80)</td>
</tr>
<tr>
<td>2</td>
<td>(±)-4 (1) Immobilized lipase (MY-30)</td>
<td>(R)-4 77 (24)</td>
<td>(S)-3 22 (85)</td>
</tr>
<tr>
<td>3</td>
<td>(±)-4 (1) OF-360</td>
<td>(R)-4 38 (83)</td>
<td>(S)-3 60 (51)</td>
</tr>
<tr>
<td>4</td>
<td>(±)-4 (1) Immobilized lipase (OF-360)</td>
<td>(R)-4 40 (90)</td>
<td>(S)-3 52 (58)</td>
</tr>
<tr>
<td>5</td>
<td>(±)-4 (0.4) OF-360</td>
<td>(S)-4 74 (90)</td>
<td>(S)-3 16 (30)</td>
</tr>
</tbody>
</table>

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

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(−)-3, (−)-3 was successfully converted to the reported acid (S)-(−)-4-(p-tolyl)pentanoic acid 5.9) Catalytic hydrogenation of (S)-3 gave (S)-6, followed by treatment with tosyl chloride (TsCl) to afford the tosylate (S)-7 [[α]D +16.9° (c=0.99, MeOH)] in 83% overall yield from (S)-3. NaBH4 reduction of (S)-7 provided the 4-arylpentanoate (S)-8 [42% yield, [α]D +7.1° (c=1.32, MeOH)] and the corresponding alcohol (S)-9 [40% yield, [α]D +4.5° (c=1.68, MeOH)]. Demethylation of (S)-8 with a combination of AlCl3 and ethanethiol (EtSH),9) followed by the treatment with trifluoromethanesulfonic anhydride (Tf2O) gave the triflate (S)-10. Catalytic hydrogenation of (S)-3 gave (S)-6, followed by treatment with tosyl chloride (TsCl) to afford the tosylate (S)-7 [[α]D +16.9° (c=0.99, MeOH)] in 83% overall yield from (S)-3. NaBH4 reduction of (S)-7 provided the 4-arylpentanoate (S)-8 [42% yield, [α]D +7.1° (c=1.32, MeOH)] and the corresponding alcohol (S)-9 [40% yield, [α]D +4.5° (c=1.68, MeOH)]. Demethylation of (S)-8 with a combination of AlCl3 and ethanethiol (EtSH),9) followed by the treatment with trifluoromethanesulfonic anhydride (Tf2O) gave the triflate (S)-10, which was subjected to catalytic hydrogenolysis to afford the (−)-(p-tolyl)pentanoate (S)-11 [[α]D +29.1° (c=0.89, MeOH)] in 48% overall yield from (S)-8. An alkaline hydrolysis of (S)-11 provided a carboxylic acid (S)-5 [92% yield, [α]D +25.1° (c=0.55, MeOH) corresponding to 90% ee], of which the spectral data ([α]D) were identical to those [[α]D +29.1° (c=0.99, MeOH)] of the reported (S)-5.10) Thus the absolute configuration of the present (−)-3 was determined to be S. Then total syntheses of (S)-curcuclidic acid (S)-5 and (S)-curcuphenol (1) formally derived from (S)-2,10) were achieved from (S)-3 (90% ee) and (R)-3 (90% ee), respectively. Conversion of (S)-9 into the one-carbon homologation product (S)-13 was achieved by the standard procedure. The alcohol (S)-9 was treated with iodine in the presence of triphenylphosphine (Ph3P) to give an iodide (S)-12 [[α]D +5.8° (c=0.78, MeOH)] in 48% yield, which was reacted with NaCN in dimethylformamide (DMF) to provide a cyanide (S)-13 [[α]D −0.9° (c=1.22, MeOH)] in 99% yield. Alkaline hydrolysis of (S)-13 followed by successive esterification gave the methyl ester (S)-14 [[α]D +6.2° (c=1.15, MeOH)] in 54% overall yield from (S)-13. Demethylation of (S)-14 with a combination of AlCl3 and EtSH provided the phenol (S)-15, which was treated with Grignard reagent to afford (S)-curcuclidic acid (S)-5 and (S)-curcuphenol (1) in the literature.
phenol (R)-17 was treated with methoxymethyl chloride (MOMCl) to give the MOM ether (R)-18 [([α]D) −3.1° (c=1.88, CHCl3)] in 94% overall yield from (R)-16. Hydrolysis of (R)-18 gave an alcohol (R)-19 [([α]D) −3.9° (c=1.47, CHCl3)] in 98% yield, which was subjected to pyridinium chlorochromate (PCC) oxidation to provide an aldehyde (R)-20. The Wittig reaction of (R)-20 afforded an olefin (R)-21 [([α]D) −9.8° (c=1.01, CHCl3)] in 62% overall yield from (R)-19. Deprotection of (R)-21 gave (R)-curcumen-4 (1) [62% yield, ([α]D) −20.9° (c=1.73, CHCl3) corresponding to 90% ee], for which the spectral data ([([α]D)1H, 13C-NMR, and high-resolution mass spectra (HR-MS)] were identical with those of [([α]D)−23.6° (CHCl3)βββ] of natural product (R)-1.

Experimental

1H- and 13C-NMR spectra were recorded on JEOL EX-400 (400 MHz) or a JEOL α-500 (500 MHz) spectrometers with tetramethylsilane (TMS) as an internal standard in CDCl3. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), double doublet (dd), multiplet (m), and broad (br). Carbon substitution degrees were established by distortionless enhancement by polarization transfer (DEPT) pulse sequence. HR-MS were employed.

Deprotection of Lipase on Photo-Crosslinkable Resin Prepolymer (ENTF-4000)

Typical immobilization procedures with photocross-linkable resin prepolymer are as follows. One gram of ENTP-4000 is mixed with 10 mg of the photosensitizer benzoin ethyl ether. The mixture is melted completely at 60°C. The powdered lipase (100 mg) is added to the molten mixture under continuous mixing. The prepolymer–lipase mixture is layered on a sheet of transparent polyester film (thickness, ca. 0.5 mm). The layer is covered with transparent thin film and then illuminated with chemical lamps (wavelength range, 300—400 nm) for 3 min. The gel film thus formed is cut into small pieces (0.5×0.5×0.5 mm) and used for the bioconversion reaction.

Enzymatic Resolution of (±)-4

i) Table 1, Entry 1: A suspension of (±)-4 (0.2 g), lipase MY-30 (0.1 g) in H2O-saturated isopropl ether (10 ml) was incubated at 33°C for 3 d. This scale experiment was carried out five times simultaneously (total amount of (±)-4 was 1 g). After the reaction mixture was concentrated in a rotavapor, the precipitate was dissolved in acetone, ether, and 7% aqueous NaHCO3 were added to the reaction mixture and the organic layer was washed with saturated brine, ether, and (±)-4 (0.2 g) was isolated by washing with aqueous NaHCO3 and ether. The organic layer was evaporated to give a residue that was chromatographed on silica gel (10 g, n-hexane:AcOEt=4:1) to afford (R)-3 (0.293 g, 99%) as a homogeneous oil. The NMR data of (R)-3 were identical to those of the reported (±)-4βββ.

ii) Table 1, Entry 2: A suspension of (±)-4 (0.25 g), immobilized lipase MY-30 (0.1 g) in H2O-saturated isopropl ether (10 ml) was incubated at 33°C for 3 d. This scale experiment was carried out four times simultaneously (total amount of (±)-4 was 1 g). The reaction mixture was worked up in the same way as for i) to give (R)-4 (0.77 g, 77%, 24% ee) and (S)-3 (0.188 g, 22%, 85% ee).

iii) Table 1, Entry 3: A suspension of (±)-4 (0.2 g), lipase OF-360 (0.1 g) in H2O-saturated isopropl ether (10 ml) was incubated at 33°C for 3 d. This scale experiment was carried out five times simultaneously (total amount of (±)-4 was 1 g). The reaction mixture was worked up in the same way as for i) to give (R)-4 (0.38 g, 38%, 83% ee) and (S)-3 (0.514 g, 60%, 51% ee).

iv) Table 1, Entry 4: A suspension of (±)-4 (0.2 g), immobilized lipase OF-360 (0.1 g) in H2O-saturated isopropl ether (10 ml) was incubated at 33°C for 3 d. This scale experiment was carried out five times simultaneously (total amount of (±)-4 was 1 g). The reaction mixture was worked up in the same way as for i) to give (R)-4 (0.43 g, 40%, 90% ee) and (S)-3 (0.445 g, 52%, 58% ee).

v) Table 1, Entry 5: A suspension of (S)-3 (80% ee, 0.2 g), lipase OF-360 (0.1 g) and isopropl acetate (0.2 g) in isopropl ether (10 ml) was incubated at 33°C for 3 d. This scale experiment was carried out two times simultaneously (total amount of (S)-3 was 0.4 g). The reaction mixture was worked up in the same way as for i) to give (S)-4 [0.346 g, 74%, [([α]D)βββ+7.2° (c=0.46, MeOH)] corresponding to 90% ee] and (S)-3 (0.064 g, 16%, 30% ee).
(45)-4-(Methylphenyl)pentanoic Acid (5) A solution of (S)-11 (0.064 g, 0.31 mmol) and 2 m aqueous NaOH (1 ml) in MeOH (2 ml) was stirred at 50 °C for 1 h. After the reaction mixture was diluted with H2O and ether, the water layer was acidified with 2 m aqueous HC1 and extracted with ether. The organic layer was washed with saturated brine and dried over MgSO4. Evaporation of the organic solvent gave an acid (S)-5 (0.055 g, 92%) as a homogeneous oil. (S)-5: [α]25D = +25.1° (c= 0.55, MeOH; corresp. to 90% ee); NMR: δ 1.25 (3H, d, J = 7.1 Hz), 1.81–1.96 (2H, m), 2.17–2.25 (2H, m), 2.30 (3H, s), 2.69 (1H, q, J = 13.2 Hz), 7.05 (2H, d, J = 8.2 Hz), 7.10 (2H, d, J = 8.2 Hz). HR-MS (EI) Calcd for C13H20O (M+, m/z): 192.1150. Found: 192.1129.

1-Lodo-(4S)-2-(methoxy-4-methylphenyl)pentane (12) Triphenylphosphine (Ph3P, 0.79 g, 3 mmol), imidazole (0.26 g, 3.7 mmol) and iodine (0.9 g, 3.7 mmol) were added to a solution of (S)-9 (0.312 g, 1.5 mmol) in Et2O (5 ml) at 0 °C and the whole mixture was stirred for 0.5 h at room temperature. The reaction mixture was filtered with the aid of Celite and the filtrate was evaporated to give a residue that was chromatographed on silica gel (10 g, n-hexane:AcOEt=100:1) to afford (S)-12 (0.229 g, 48%) as a homogeneous oil. (S)-12: [α]25D = +5.8° (c= 0.78, MeOH). The NMR data of (S)-12 were identical to those of the reported (12).3,5

(4S)-2-(Methoxy-4-methylphenyl)hexanenitrile (13) A solution of (S)-9 (0.287 g, 0.85 mmol) in DMF (1 ml) was treated with NaCN (0.06 g, 1.91 mmol) and then allowed to cool. After ether was added to the reaction mixture, the ether layer was washed with saturated brine and dried over MgSO4. The organic layer was evaporated to give a residue that was chromatographed on silica gel (10 g, n-hexane:AcOEt=5:1) to afford (S)-13 (0.164 g, 0.58 mmol) in MeOH (1 ml) was treated with 2 m aqueous NaOH (0.5 ml) and the whole mixture was warmed at 50 °C for 10 min, and then allowed to cool. After ether was added to the reaction mixture, the ether layer was washed with saturated brine and dried over MgSO4. The organic layer was evaporated to give a residue that was chromatographed on silica gel (10 g, n-hexane:AcOEt=5:1) to afford (R)-19 (0.136 g, 98%) as a homogeneous oil. (R)-19: [α]25D = −3.9° (c= 1.47, CHCl3). The NMR data of (R)-19 were identical to those of the reported (19).3,5

Protected (4R)-curcuphenol (21) i) PCC (0.67 g, 3.1 mmol) was added to a mixture of (R)-19 (0.147 g, 0.62 mmol) and Celite 545 (2 g) in CH2Cl2 (5 ml) at 0 °C. The reaction mixture was stirred for 1 h at room temperature and then allowed to cool. The filtrate was washed with 10% NaHCl to afford (R)-21 (0.10 g, 62% overall yield) as a homogeneous oil. (R)-21: [α]25D = −9.8° (c= 1.01, CHCl3). The NMR data of (R)-21 were identical to those of the reported (21).3,5

(R)-Curcuphenol (1) A mixture of 2 m aqueous HCl (1 ml) and isopropanol (1 ml) was added to a solution of (R)-21 (0.1 g, 0.38 mmol) in isopropanol (0.5 ml). The whole reaction mixture was warmed at 60 °C for 30 min. After ether was added to the reaction mixture, the ether layer was washed with saturated brine and dried over MgSO4. The organic layer was evaporated to give a residue that was chromatographed on silica gel (10 g, n-hexane:AcOEt=5:1) to afford (R)-1 (0.052 g, 62%) as a homogeneous oil. (R)-1: [α]25D = −20.9° (c= 1.73, CHCl3). HR-MS Calcd for C13H20O (M+, m/z): 218.1617. Found: 218.1689. The spectral data (1H, 13C-NMR, IR, HR-MS) were identical with those of the reported (R)-1.3,5

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References and Notes
1) A part of this work was published as a preliminary communication: Ono M., Ogura Y., Hatogai K., Akita H., Tetrahedron: Asymmetry, 6, 1829–1832 (1995).