Note

Enzymatic Synthesis of (S)-2-(6-Benzxyloxy-2,5,7,8-tetramethyl-2-chromanyl)ethanol, Intermediate for the Synthesis of Vitamin E

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Racemic 2-(6-benzyloxy-2,5,7,8-tetramethyl-2-chromanyl)ethanol (5) was successfully resolved by employing asymmetric benzoylation and lipoprotein lipase (LPL). (S)-5 was obtained with more than 99% e.e.

Vitamin E, (2R,4'R,8'R)-α-tocopherol I is a potent antioxidant and radical scavenger. Some previous works exploring the relationship between the antioxidative activity and the stereochemistry of tocopherol have revealed that the (2R)-configuration played an important role in the activity. Syntheses of tocopherol or chroman skeletons of naturally occurring form have already been reported by many workers. In the course of our studies on biotransformation with enzymes, we were intrigued by an alternative and more effective approach for synthesizing (S)-2-(6-benzyloxy-2,5,7,8-tetramethyl-2-chromanyl)ethanol, the intermediate for the synthesis of vitamin E, by an enzymatic method. In this report, the optical resolution of racemic 2-(6-benzyloxy-2,5,7,8-tetramethyl-2-chromanyl)ethanol is described.

The reaction of triol 2 and trimethylhydroquinone 3 in toluene-dioxane in the presence of ZnCl2 and a small amount of hydrochloric acid provided alcohol 4 in a 47% yield. For the purpose of simplifying the enzymatic reactions and stabilizing the substrate, the phenolic hydroxy group was protected as benzy ether 5, which was then transformed to benzoate 6 in the usual manner.

The optical resolution of benzoate 6 was determined by examining the asymmetric hydrolytic activities of some lipases and microorganisms.

Benzoate 6 recovered unchanged from the hydrolysis by LPL (Kyowa) had a relatively high optical purity. LIP (Asahi Chemical) and several microorganisms were also hydrolyzed, but they each showed low enantioselectivity. From these findings, LPL was selected for use in further investigations.

The optical purity of benzoate 6 was analyzed by HPLC, using Chiralcel OD (Daicel), and that of alcohol 5 was measured after converting to the corresponding benzoate.

The absolute configuration was next determined. After the asymmetric hydrolysis of benzoate 6 by LPL, the recovered benzoate was hydrolyzed by sodium hydroxide. Swern oxidation of the alcohol then gave aldehyde 7, which showed [α]D + 8.5° (CHCl3). The specific rotation for the aldehyde with (S)-configuration has been reported to be [α]D + 16.2° (CHCl3). This result indicates that recovered benzoate 6 would have had the desired (S)-configuration.

The optical resolution by employing acylation with LPL was also investigated. Benzoylation of alcohol 5 catalyzed by LPL was attempted in toluene-tetrahydrofuran with benzoic anhydride as an acyl donor, the experiment resulting in the (S)-alcohol remaining unchanged and the (R)-alcohol being benzoylated as expected. After 3.5h of incubation, the optical purity of the (S)-alcohol reached more than 99% e.e., and the yield was 30%.

In summary, alcohol 5 was obtained via optical resolution with lipoprotein lipase (Kyowa) with more than 99% e.e. The overall yield in the three steps was about 13%.

Experimental

IR spectra were recorded with a JASCO IR-810 instrument, and proton NMR spectra were obtained with JEOL FX-100 and PS-100 instruments. Chemical shifts are reported in parts per million (ppm) relative to TMS as an internal standard. Optical rotation values were recorded with a...
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<td>Enzyme</td>
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<td>50</td>
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To 2 ml of a 0.1M potassium phosphate buffer at pH 7.0 containing Triton X-100 (0.5%) was added a solution of benzoyl (6) (30 mg) in DMF (60 μl) and an enzyme, and the mixture was stirred at 30°C.

JASCO digital polarimeter, and HRMS spectra were obtained with a JEOL JMS-HX-110A instrument. HPLC analyses of optical purity were performed with a JASCO Triathion system, using a Chiralcel OD column (4.6 mm × 250 mm) monitored at 254 nm and eluting with 9:1 hex-ane-ethanol at a flow rate of 0.4 ml/min. The HPLC retention time of benzoyl 6 with the (S)-configuration was 15.4 min and that with (R) was 16.3 min.

2-(6-Hydroxy)-2,5,7,8-tetramethyl-2-chromanoyl)ethanol (4). To a suspension of 10 g of trimethylhydroquinone (1) and 100 ml of toluene was added 5 g of anhydrous ZnCl₂. After heating this suspension at 100°C, a solution of 17.6 g of 3-methyl-3,5-pentanetiol in 80 ml of dioxane and 10 ml of 6% hydrochloric acid was successively added, and the mixture was stirred for 6 hr. After being cooled to a room temperature, the reaction mixture was poured into water and extracted three times withethyl acetate. The organic phase was successively washed with water, saturated NaHCO₃, and brine, and dried over Na₂SO₄. After evaporating the solvent, the residue was purified by silica gel column chromatography to give 7.8 g of 4 as a viscous oil (47% yield). 1H-NMR (CDCl₃): δ: 1.28 (3H, s), 1.6-2.2 (4H, m), 2.08 (3H, s), 2.10 (3H, s), 2.15 (3H, s), 2.62 (2H, t, J = 7 Hz), 3.90 (2H, t, J = 7 Hz), 4.43 (2H, s), 4.69 (1H, t, J = 3 Hz), 2.60 (1H, s), 1.40 (3H, s), 1.38 (3H, s), 1.26 (3H, s), 1.12 (6H, s), 1.00 (6H, s), 1.00 (6H, s). HRMS m/z (M⁺): calcd. for C₁₅H₂₂O₄, 250.1570; found, 250.1561.

2-(6-Benzoyloxy)-2,5,7,8-tetramethyl-2-chromanoyl)ethanol (5). To a solution of 4 (1 g) in acetonitrile (30 ml) were added 1.5 ml of benzyl bromide and 1.6 g of potassium carbonate, and the mixture was stirred under reflux for 16 hr. The mixture was cooled to room temperature, concentrated, diluted with water and extracted three times with ethyl acetate. The organic phase was washed with brine and concentrated, and the residue was purified by silica gel column chromatography to afford 1.3 g of an oily compound (98% yield). 1H-NMR (CDCl₃): δ: 1.28 (3H, s), 2.03 (3H, s), 2.16 (3H, s), 2.21 (3H, s), 1.6-2.2 (4H, m), 2.64 (2H, t, J = 7 Hz), 3.90 (2H, t, J = 7 Hz), 4.68 (2H, s), 7.2-7.6 (5H, m), 1500 (m), 1460 (s), 1415 (s), 1375 (s), 1255 (s), 1170 (s), 1090 (s), 1060 (s), 1020 (m), 920 (m), 755 (m), 740 (s), 700 (s). HRMS m/z (M⁺): calcd. for C₂₀H₂₇O₄, 340.2039; found, 340.2054.

Hydrolysis of benzoyl 6 by LPL. A solution of 6 (2.5 g) in N,N-dimethylformamide (6 ml) was added to 0.1 M potassium phosphate buffer at pH 7.0 containing 0.5% Triton X-100 (300 ml), a suspension of lipoprotein lipase (125 mg) was then added, and the mixture was stirred for 24 hr at 30°C. After being saturated with sodium chloride, the reaction mixture was filtered through a Celite pad, and the filtrate was extracted three times with ethyl acetate. The organic phase was washed with brine, dried over magnesium sulfate and then concentrated. The residue was purified by silica gel column chromatography to give 0.36 g of benzoyl 6 (39% yield, 91% e.e.) and 1.1 g of alcohol 5 (60% yield, 57% e.e.).

Physical data for optically active 6: 1H-NMR (CDCl₃): δ: 1.39 (3H, s), 2.13 (3H, s), 2.21 (3H, s), 2.24 (3H, s), 1.8-2.2 (4H, m), 2.68 (2H, t, J = 8 Hz), 4.56 (2H, d, J = 4, 8 Hz), 5.75 (2H, s), 7.3-8.3 (10H, m), IR vₚₖₘ, cm⁻¹: 2930 (s), 1720 (s), 1695 (m), 1605 (m), 1585 (m), 1500 (m), 1455 (s), 1415 (s), 1380 (s), 1230 (s), 1255 (s), 1255 (s), 1219 (m), 1180 (m), 1160 (m), 1115 (s), 1095 (s), 740 (m), 715 (s), 700 (s). [α]D₂ = +2.26 (CHCl₃, ε = 1.2). HRMS m/z (M⁺): calcd. for C₁₉H₂₅O₄, 442.2301; found, 444.2293. The NMR and IR spectra of alcohol 5 were identical with those data already described; [α]D₂ = −8.11 (CHCl₃, ε = 1.15).

Asymmetric benzoxazinol of 5 by LPL. Lipoprotein lipase (15 mg) and benzoic anhydride (90 mg) were added to a solution of 5 (50 mg) in toluene (3 ml) and tetrahydrofuran (0.5 ml), and the mixture was stirred at room temperature for 1 hr. The reaction mixture was filtered, and successively washed with saturated NaHCO₃ and brine, and then concentrated. The residue was purified by silica gel column chromatography to give benzoyl 6 and 115 mg of alcohol 5 (31% yield). The NMR and IR spectra of alcohol 5 were identical with those described above.

References