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Chemoenzymatic enantioselective synthesis of (1*S*,5*R*)-(−)-frontalin

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Abstract—The pheromone (1*S*,5*R*)-(−)-frontalin was synthesized in 90% e.e. via a chemoenzymatic route. The key step was the stereoselective acylation (desymmetrization) of 2-(4,5-dihydroxy-4-hydroxymethylpentyl)-2-methyl-1,3-dioxolane with vinyl acetate in organic media in the presence of *Pseudomonas* sp. lipase.

1. Introduction

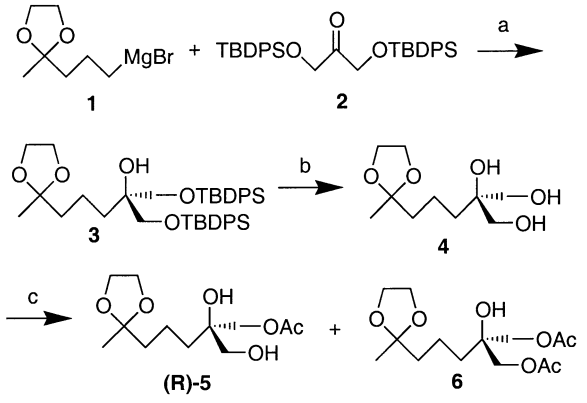
Frontalin (1,5-dimethyl-6,8-dioxabicyclo[3,2,1]octane) is the aggregation pheromone of pine beetles of the Dendroctonus family.[1,2] Frontalin was also isolated from the temporal gland secretion in the male Asian elephant during the condition of musth[3] and frontalin has recently been identified in the bark of several angiosperm trees.[4] The ecological role of frontalin in trees that are not hosts for the insects using this pheromone is still unknown. Frontalin from the pine beetle *Dendroctonus frontalis* is an 85:15 mixture of (1*S*,5*R*)- and (1*R*,5*S*)-enantiomers. Bioassays have shown that the (1*S*,5*R*)-(−) enantiomer of frontalin is much more active than the (1*R*,5*S*)-(+)-enantiomer.[2,5] Pheromones have been successfully used in strategies to control the progression of pine beetle infestations in forests.[6]

Frontalin is a valuable simple target to test diverse enantioselective synthetic methods. Many syntheses of frontalin have been reported[7] but only a few chemoenzymatic syntheses have been achieved. The biotransformations involved in these chemoenzymatic syntheses were hydrolase-catalyzed kinetic resolutions[7h] of racemates or enantioselective reductions with microorganisms.[7i] Herein, we describe an enantioselective synthesis of (−)-frontalin via the enzymatic desymmetrization of an achiral substrate.

2. Results and discussion

Retrosynthetic analysis of the frontalin structure suggested that the prochiral triol **4** might serve as a suitable substrate for an enzyme-catalyzed desymmetrization. Synthesis and desymmetrization of triol **4** are described in Scheme 1. Addition of the Grignard reagent **1** prepared from the ethylene acetal of 5-bromo-2-pentanone[8] to the dihydroxyacetone derivative **2**[9] in THF provided tertiary alcohol **3** in 86% yield. Desilylation of **3** with tetrabutylammonium fluoride (TBAF) afforded triol **4** in 90% yield.

Next, we completed some screening experiments to find enzymes with the ability to distinguish the enantiotopic groups of compound **4**. Of the enzymes and conditions studied, the esterification of triol **4** with vinyl acetate in



Scheme 1. *Reagents and conditions*: (a) THF −78°C; (b) TBAF, THF; (c) *Pseudomonas* sp. lipase, vinyl acetate, benzene.

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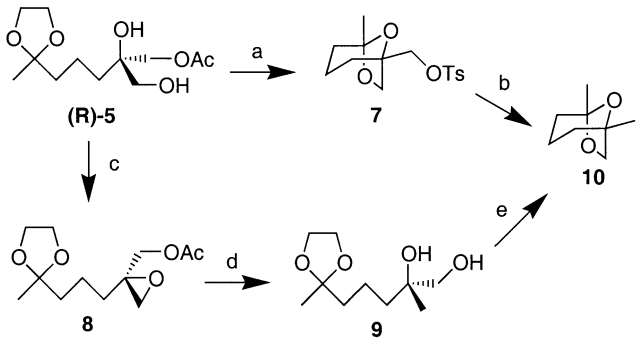

Scheme 2. *Reagents and conditions*: (a) (i) TsCl, DMAP, pyridine, (ii) TsOH, CH_2Cl_2, H_2O; (b) $LiEt_3BH$, THF, reflux; (c) TsCl, Et_3N, DMAP, CH_2Cl_2; (d) $LiAlH_4$, THF; (e) TsOH, Et_2O, H_2O.

the presence of *Pseudomonas* sp. lipase (lipase AK) in benzene gave enantiomerically enriched monoester (*R*)-(−)-**5** (45% yield) and the corresponding achiral diester **6** (55% yield). The reaction was monitored by TLC analysis and terminated when all the starting material **4** was consumed. The enzymatic reaction was fast and regioselective for the primary alcohol and stereoselective. However, the monoacetate **5** also acted as a substrate for the enzyme and thus the acylation reaction also afforded diester **6** leading to only moderate yield of monoester **5**. The enantiomeric composition of **5** (e.e.= 90%) was determined by reaction with (*R*)-(−)-acetoxyphenylacetic acid in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) and dimethylaminopyridine (DMAP), followed by NMR analysis (300 MHz) of the resulting diastereomeric esters. The absolute configuration of monoester **5** was established by its transformation into (1*S*,5*R*)-(−)-frontalin.

Monoester (*R*)-**5** provided a multifunctional intermediate that can be transformed into frontalin by two routes differing in the timing of the reduction of the hydroxymethyl group to the 1-methyl group (Scheme 2). Monoester (*R*)-**5** was treated with tosyl chloride in pyridine and acid-catalyzed intramolecular transacetalization of the resulting crude tosylate provided bicyclic compound (1*S*,5*R*)-**7** in 93% yield. Reduction of **7** with lithium triethylborohydride following the procedure reported by Monneret et al.[10] gave (1*S*,5*R*)-(−)-frontalin in 95% yield.

The alternative route to frontalin is illustrated in Scheme 2. Formation of the tosylate in the presence of a stronger base such as triethylamine afforded epoxide (*R*)-**8** (yield: 90%). Double reduction of epoxy-ester **8** with $LiAlH_4$ gave the diol (*S*)-**9** in 90% yield. Hydrolysis of **9** under acidic conditions gave the corresponding dihydroxyketone, which underwent intramolecular acetalization to yield (1*S*,5*R*)-(−)-frontalin **10** (yield: 92%) ($[\alpha]_D^{25}$ −52.1 (*c* 0.5, Et_2O); lit.[7i] $[\alpha]_D^{25}$ −50.3 (*c* 1.63, Et_2O)).

In summary, a synthesis of (−)-frontalin based on the enantioselective enzyme-catalyzed acylation of a prochiral substrate was accomplished in five steps giving 31% overall yield (six steps and 26% overall yield for the alternative reactions sequence).

3. Experimental

3.1. General

Optical rotations were measured using a JASCO DIP-360 digital polarimeter. NMR spectra were recorded at 300 MHz (^1H) and 75 MHz (^{13}C) on a Bruker AC-300 instrument. Infrared spectra were recorded on a Bomem MB-100 spectrometer. Flash column chromatography was carried out using 40–63 μm (230–400 mesh) silica gel. Lipase from *Pseudomonas* sp. (lipase AK) was purchased from Amano.

3.2. 2-(5-*tert*-Butyldiphenylsiloxy-4-*tert*-butyldiphenylsiloxymethyl-4-hydroxypentyl)-2-methyl-1,3-dioxolane 3

A solution of the ethylene ketal of 5-bromo-2-pentanone (7.76 g, 37.1 mmol) and methyl iodide (200 μL) in dry THF (30 mL) was added dropwise to a slurry of magnesium (2.70 g, 111.1 mmol) in THF (10 mL). The mixture was stirred at room temperature for 30 min. The mixture was cooled to −78°C and a solution of ketone **2** (6.56 g, 11.57 mmol) in THF (45 mL) was added dropwise. The resulting mixture was stirred at −78°C for 6 h and allowed to warm to 0°C at which time saturated NH_4Cl (500 mL) was added dropwise. The mixture was extracted with ethyl acetate (3×500 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (ether–hexane, gradient 1/19 to 1/4) to give **3** as a white solid (6.95 g, 86%). Mp 75–76°C (from hexane); IR (KBr) 3580–3260, 1418, 1207, 806, 690, 675 cm^{-1}; ^1H NMR ($CDCl_3$) 7.66–7.74 (m, 8H), 7.34–7.46 (m, 12H), 3.90 (m, 4H), 3.72 (d, J=9.7 Hz, 2H), 3.64 (d, J=9.7 Hz, 2H), 2.43 (br s, 1H), 1.40–1.64 (m, 6H), 1.30 (s, 3H), 1.07 (s, 18H); ^{13}C NMR ($CDCl_3$) 135.5, 133.1, 129.6, 127.6, 109.9, 74.4, 65.9, 64.5, 39.7, 33.8, 26.8, 23.6, 19.2, 17.3; HRMS (CI, NH_3) calcd for $C_{40}H_{51}O_3Si_2$ ($M-C_2H_5O_2$): 635.3377. Found: 635.3352.

3.3. 2-(4,5-Dihydroxy-4-hydroxymethylpentyl)-2-methyl-1,3-dioxolane 4

Compound **3** (1.17 g, 1.68 mmol) in 6 mL of dry THF was treated with tetrabutylammonium fluoride (1 M in THF, 5.2 mL, 5.2 mmol) at room temperature for 5 h. The solvent was evaporated and the crude product was purified by flash chromatography (ethyl acetate–hexane, 1/3, to ethyl acetate–methanol, 9/1) to yield **4** as a colorless oil (329 mg, 90%). IR (neat) 3350, 2920, 1366, 1210, 1036 cm^{-1}; ^1H NMR ($CDCl_3$) 4.06 (br s, 3H), 3.91 (m, 4H), 3.63 (d, J=11.2 Hz, 2H), 3.56 (d, J=11.2 Hz, 2H), 1.61 (m, 2H), 1.42 (m, 4H), 1.28 (s, 3H); ^{13}C NMR ($CDCl_3$) 109.8, 74.3, 66.6, 64.5, 39.4, 34.5, 23.6, 17.4; HRMS (CI, NH_3) calcd for $C_9H_{17}O_5$ ($M-CH_3$): 205.1076. Found: 205.1081.

3.4. (*R*)-2-(4-Acetoxymethyl-4,5-dihydroxypentyl)-2-methyl-1,3-dioxolane 5

Compound **4** (302 mg, 1.37 mmol) was dissolved in 35 mL of dry benzene containing 300 mg of 4 Å molecular sieves. Vinyl acetate (675 μL, 7.32 mmol) and crude *Pseudomonas* sp. lipase (700 mg) were added and the mixture was stirred for 1.5 h at room temperature; it was then filtered and the solids were washed with ether. The solvents were evaporated and the crude product was purified by flash chromatography (ethyl acetate–hexane, 1/1, to ethyl acetate–methanol, 4/1) to provide monoester **5** (160 mg, 45%) and the corresponding diester **6** (232 mg, 55%). Compound **5**: $[\alpha]_D^{23}$ −2.6 (*c* 2.3, acetone); IR (neat) 3380, 2930, 2875, 1712, 1450, 1368, 1235, 1138, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) 4.12 (d, $J=11.5$ Hz, 1H), 4.01 (d, $J=11.5$ Hz, 1H), 3.92 (m, 4H), 3.48 (d, $J=11.5$ Hz, 1H), 3.42 (d, $J=11.5$ Hz, 1H), 2.57 and 2.67 (br s, 2H), 2.09 (s, 3H), 1.63 (m, 2H), 1.48 (m, 4H), 1.29 (s, 3H); ^{13}C NMR ($CDCl_3$) 171.5, 109.8, 73.3, 66.4, 65.2, 64.5, 39.3, 34.2, 23.6, 20.7, 17.2; HRMS (CI, NH_3) calcd for $C_{12}H_{26}O_6N$ (M+NH_4): 280.1760. Found: 280.1764. Compound **6**: IR (neat) 3468, 2959, 2884, 1743, 1464, 1436, 1376, 1236, 1044 cm^{-1}; ^1H NMR ($CDCl_3$) 4.04 (m, 4H), 3.91 (m, 4H), 2.08 (s, 6H), 1.64 (m, 2H), 1.53 (m, 4H), 1.29 (s, 3H); ^{13}C NMR ($CDCl_3$) 170.8, 109.7, 72.2, 66.6, 64.5, 39.3, 34.6, 23.7, 20.7, 17.0; HRMS (CI, NH_3) calcd for $C_{14}H_{28}O_7N$ (M+NH_4): 322.1866. Found: 322.1869.

3.5. (1*S*,5*R*)-5-Methyl-1-*para*-toluenesulfonyloxymethyl-6,8-dioxabicyclo[3,2,1]octane 7

A solution of compound **5** (112.5 mg, 0.430 mmol), *p*-toluenesulfonyl chloride (163.6 mg, 0.859 mmol) and 4-dimethylaminopyridine (10 mg) in dry pyridine (2 mL) was stirred for 24 h at room temperature. Ether (100 mL) was added and the organic layer was washed with a 1N HCl solution (3×100 mL), with a saturated $NaHCO_3$ solution (3×100 mL) and with brine (3×100 mL), dried, and evaporated. A mixture of the crude tosylate (153 mg, 0.367 mmol), water (100 μL), *p*-toluenesulfonic acid monohydrate (105 mg, 0.552 mmol) and CH_2Cl_2 (2 mL) was stirred at room temperature for 72 h. Ether (50 mL) was added and the organic layer was washed with saturated $NaHCO_3$ (3×50 mL), water (3×50 mL), dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (ethyl acetate–hexane, 1/4 to 4/1) to give tosylate **7** (106.6 mg, 93%) as a white solid. Mp 103–104°C (from hexane); $[\alpha]_D^{23}$ −18.2 (*c* 1.32, $CHCl_3$); lit.[10]: mp 110°C, $[\alpha]_D^{20}$ −20 (solvent and concentration not specified); IR (KBr) 1360, 1193, 1174, 975, 843, 819, 556, 524 cm^{-1}; ^1H NMR ($CDCl_3$) 7.72 (d, $J=8$ Hz, 2H), 7.28 (d, $J=8$ Hz, 2H), 3.98 (d, $J=10$ Hz, 1H), 3.96 (d, $J=10$ Hz, 1H), 3.82 (d, $J=7$ Hz, 1H), 3.44 (d, $J=7$ Hz, 1H), 2.38 (s, 3H), 1.46–1.87 (m, 6H), 1.30 (s, 3H); ^{13}C NMR ($CDCl_3$) 144.9, 132.5, 129.7, 127.9, 109.0, 80.1, 71.6, 70.5, 34.4, 29.0, 24.1, 21.5, 17.0.

3.6. (1*S*,5*R*)-(−)-1,5-Dimethyl-6,8-dioxabicyclo[3,2,1]-octane or (1*S*)-(−)-frontalin 10

A 1 M solution of lithium triethylborohydride in THF (4 mL) was added to a cold (0°C) solution of tosylate **7** (45 mg, 0.144 mmol) in dry THF. The mixture was heated at reflux for 3 h. The mixture was allowed to cool to room temperature and then poured into ice-water (3 mL). The solution was acidified with 1N HCl and extracted with ether. The extracts were washed with 1N HCl, saturated $NaHCO_3$, water, dried ($MgSO_4$), and concentrated without the application of heat. The crude product was purified by flash chromatography (hexane) to yield (−)-frontaline **10** (19.5 mg, 95%) as a colorless oil. $[\alpha]_D^{23}$ −52.0 (*c* 0.5, ether); lit.:[10] $[\alpha]_D^{20}$ −52 (*c* 1, ether). Spectroscopic data were identical to those reported in the literature.

3.7. (*R*)-2-(4-Acetoxymethyl-4,5-epoxypentyl)-2-methyl-1,3-dioxolane 8

Triethylamine (1.5 mL, 10.8 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (5 mg) were added to a solution of diol **5** (156 mg, 0.595 mmol) in anhydrous methylene chloride (10 mL). Tosyl chloride (370 mg, 1.94 mmol) was added and the solution was stirred at room temperature for 7 days. Ether (100 mL) was added and the organic phase was washed with 1N HCl, saturated $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (hexane–ethyl acetate–triethylamine, 74/25/1) to give **8** as a colorless oil (130 mg, 90%). $[\alpha]_D^{23}$ −6.0 (*c* 1.84, acetone); IR (neat) 3053, 1743, 1241, 1227, 1041 cm^{-1}; ^1H NMR ($CDCl_3$) 4.24 (d, $J=12$ Hz, 1H), 3.93 (d, $J=12$ Hz, 1H), 3.87 (m, 4H), 2.69 (d, $J=5$ Hz, 1H), 2.65 (d, $J=5$ Hz, 1H), 2.02 (s, 3H), 1.43–1.80 (m, 6H), 1.22 (s, 3H); ^{13}C NMR ($CDCl_3$ 170.5, 110.1, 66.3, 65.1, 57.5, 50.4, 39.6, 32.5, 23.9, 20.5, 19.8; HRMS (CI, NH_3) calcd for $C_{12}H_{21}O_5$ (M+H): 245.1389. Found: 245.1395.

3.8. (*S*)-2-(4,5-Dihydroxy-4-methylpentyl)-2-methyl-1,3-dioxolane 9

Epoxide **8** (44.8 mg, 0.183 mmol) was dissolved in anhydrous THF (1 mL) under N_2, $LiAlH_4$ (28 mg, 0.74 mmol) was added and the mixture was stirred at room temperature for 1 h. Ether (20 mL) was added and the reaction was quenched with sodium sulfate monohydrate. The mixture was filtered through Celite and the solvent was evaporated. The crude product was purified by flash chromatography (ethyl acetate–hexane, 1/4, to pure ethyl acetate) to give **9** as a colorless oil (33.4 mg, 90%). $[\alpha]_D^{23}$ −2.1 (*c* 1.2, ether); lit.:[11] $[\alpha]_D^{25}$ −1.8 (*c* 1.2, ether); IR (neat) 3583, 3410, 1378, 1152, 1055 cm^{-1}; ^1H NMR ($CDCl_3$) 3.55 (m, 4H), 3.34 (d, $J=11$ Hz, 1H), 3.28 (d, $J=11$ Hz, 1H), 2.47–2.65 (br s, 2H), 1.32–1.76 (m, 6H), 1.32 (s, 3H), 1.08 (s, 3H); ^{13}C NMR ($CDCl_3$) 110.2, 72.7, 70.0, 64.6, 40.2, 39.1, 24.0, 23.4, 18.6.

3.9. Synthesis of (−)-frontalin 10 from diol 9

A mixture of diol **9** (24 mg, 0.12 mmol), ether (5 mL), water (100 μL) and *p*-toluenesulfonic acid (3.0 mg, 0.016 mmol) was stirred at room temperature for 24 h. Ether (25 mL) was added and the organic layer was washed with saturated $NaHCO_3$ (2×25 mL), water (2× 25 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography (hexane) to yield (−)-frontaline (15.6 mg, 0.11 mmol, 92%) as a colorless oil. $[\alpha]_D^{23}$ −52.1 (*c* 0.5, Et_2O); lit.[11] $[\alpha]_D^{25}$ −51.5 (*c* 1.2, ether). Spectroscopic data were identical to those reported in the literature.

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