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ENZYMATIC KINETIC RESOLUTION OF CYANOHYDRIN ACETATES AND ITS APPLICATION TO THE SYNTHESIS OF (S)-(-)-FRONTALIN

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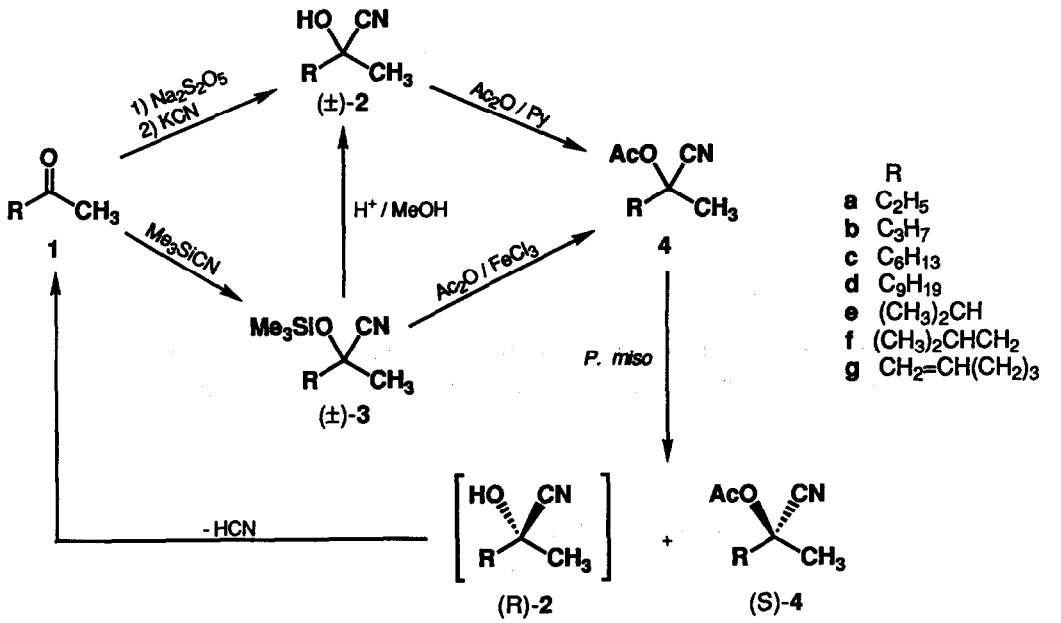
Abstract: Kinetic resolution of racemic 1-cyano-1-methylalkyl and alkenyl acetates has been achieved on incubation with Pichia miso IAM 4682, which hydrolyzed selectively the (R)-enantiomer, leaving behind the (S)-enantiomer intact. The chiral 1-cyano-1-methyl-5-hexenyl acetate thus obtained was converted to (S)-(-)-frontalin via unsaturated diol.

The enzymatic kinetic resolution of cyanohydrin acetates is unique because hydrolyzed cyanohydrin can be easily converted to starting ketone simply by controlling the pH of the medium.[1] Thus, in principle, one mole of chiral cyanohydrin acetate can be obtained from one mole of racemate without any tedious racemization process. This reaction provides a convenient tool for the synthesis of optically active compounds. Although some methods have been disclosed for the preparation of chiral aldehyde cyanohydrins including biochemical,[2] catalytic[3] and diastereoselective reactions,[4] relatively few reports have been demonstrated so far on the synthesis of ketone cyanohydrins.[5] As these compounds are considered to be useful in organic synthesis, we tried to obtain them via microbial kinetic resolution of the corresponding acetates.

We have already reported that esterases of Candida tropicalis[6] and Bacillus coagulans[7] are effective to the enantioselective hydrolysis of a number of cyanohydrin carboxylates. Thus, we first tested these strains to the kinetic resolution of 1-cyano-1-methyldecyl acetate (**4d**) as the representative substrate. Unfortu-



Scheme 1

Table 1. Microbial Hydrolysis of Ketone Cyanohydrin Acetates[a]

R	Cult (day)	Recovery (%)	$[\alpha]_D$(°)[b]	e.e. (%)
C_2H_5	0.5	25	-	0
C_3H_7	0.5	28	-15.0 (1.32, 26)	>95[c]
C_6H_{13}	2	38	-19.7 (1.28, 22)	>95[c]
C_9H_{19}	2	39	-16.7 (1.50, 29)	>95[c]
$(CH_3)_2CH$	0.5	35	+3.9 (0.56, 24)	9[c]
$(CH_3)_2CHCH_2$	0.5	28	-10.8 (1.07, 23)	90[c]
$CH_2=CH(CH_2)_3$	2	32	-24.5	>99[d]

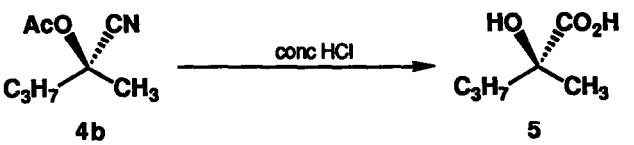
[a] Incubation was carried out at 30°C with substrate concentration of 0.3% to the medium.
[b] The concentration (c) and the temperature are shown in the parentheses.
[c] Determined by ^{1}H-NMR (90 MHz) in the presence of Eu(tfc)$_3$.
[d] Determined by ^{1}H-NMR (400 MHz) in the presence of Eu(tfc)$_3$.

nately, although hydrolysis reaction did proceed, the enantioselectivity was poor. Then, more profitable microorganisms and enzymes were screened among our type cultures and it was found that Pichia miso IAM 4682 had the highest enantioselectivity in the hydrolysis of (±)-**4d**. A sterilized nutrient medium was inoculated with P. miso and shaken for two days at 30°C. To the suspension of grown cells of the yeast, racemic acetate **4** was added and incubated for a period specified in the Table 1.

Incubation of (±)-**4d** with grown cells of P. miso for 2 days afforded (S)-**4d** in 34% yield and 2-undecanone (**1d**). The ketone **1d** is considered to be originated from the decomposition of the primary hydrolysis product, cyanohydrin **2d**. The enantiomeric excess of (S)-**4d**, $[\alpha]_D^{31}$ -16.7° (c 1.49, C_6H_6), was confirmed to be over 95% by ^{1}H NMR spectrum measured in the presence of Eu(tfc)$_3$.†

To clarify the scope of the present enantioselective hydrolysis, a number of substrates were subjected to the microbial reaction. As shown in Table 1, the enzyme system of P. miso distinguished the configuration of various 1-cyano-1-methylalkyl acetates. Although the difference in bulkiness of methyl and ethyl could not be recognized by the enzyme, n-propyl group can be said to be large enough to be distinguished from a methyl group (**4b**). The reaction of **4e** was a marked contrast compared with the results of **4b** and **4f**. Chain branching on the carbon adjacent to the asymmetric center caused the loss of enantioselectivity (**4e**), although the reaction proceeded smoothly. On the other hand insertion of a methylene group between the branched carbon and asymmetric carbon brought about the regeneration of stereoselectivity (**4f**).

The absolute configurations of the recovered acetates were estimated as follows. Optically active 1-cyano-1-methylbutyl acetate (**4b**) was heated under reflux overnight in conc. hydrochloric acid. Extraction with diethyl ether and purification with preparative TLC on silica gel afforded optically active 2-hydroxy-2-methylpentanoic acid (**5**) in ca. 40% yield, which exhibited the $[\alpha]_D^{25}$ +9.53° (c 2.12, $CHCl_3$). As the specific rotation of (R)-2-hydroxy-2-methylbutanoic acid has been reported to be $[\alpha]_D^{25}$ -8.5° (c 3, $CHCl_3$),[8] the absolute configuration



4b **5**

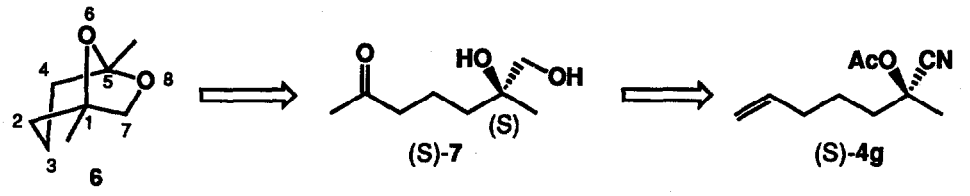
Scheme 2

of 5 was suggested to be S. In addition, comparison of ^{1}H NMR signals due to acetyl group of optically active **4b**, **c**, **d**, **f** with those of racemic compounds in the

†Eu(tfc)$_3$: Tris[3-trifluoromethylhydroxymethylene)-(-)-camphorato]europium (III).

presence of $Eu(tfc)_3$, it is concluded that the signal in the higher field always disappeared in the spectra of chiral acetates. This fact strongly suggests that the configurations of these optically active acetates are identical. Only in the case of **4e**, which has an opposite optical rotation to other acetates, the signal in the higher field was the stronger of the two due to acetyls of 2 enantiomers. Thus, the absolute configuration of recovered acetate **4b, c, d, f** were estimated to be S.

Finally, it is interesting if the cyanohydrin ester with a terminal double bond (**4g**) can be resolved in good yield because chiral **4g** is considered to be a useful starting material for the physiologically active frontalin (**6**), as shown in retrosynthetic scheme 3.

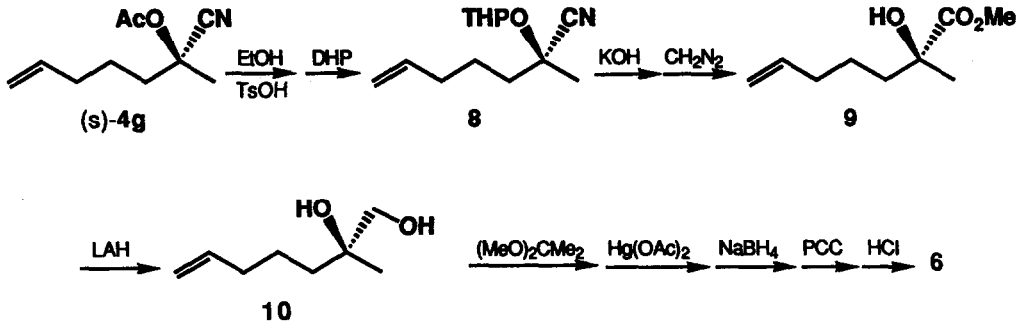


Scheme 3

Frontalin (**6**) is a component of the aggregation pheromone of females of the southern pine bark beetle, Dendroctonus frontalis and of males of western pine bark beetle, Dendroctonus brevicomis.[9] It is well established that only (1S,5R) isomer is physiologically active.[10] A number of syntheses of natural frontalin have been reported, based on enantioselective reactions,[11] starting from naturally occurring chiral precursors,[12] including optical resolution,[13] and by the aid of a microorganism.[14] Although frontalin contains two asymmetric carbons, only the (1S) center needs to be considered since the correct configuration at C-5 is dictated by the chirality of this carbon center during the formation of the acetal ring. Accordingly the synthesis of natural frontalin can be replaced by the synthesis of (S)-ketodiol **7**. Because the asymmetric diol moiety would be derived from cyanohydrin group and the partial structure of methyl ketone can be constructed from terminal olefin, the key step of the present synthesis is enzymatic resolution of 1-cyano-1-methyl-5-hexenyl acetate (**4g**). The substrate **4g** was prepared from 6-hexen-2-one (**1g**)[15] via reaction with trimethylsilyl cyanide,[16] followed by desilylation with acidic methanol and acetylation of generated free hydroxyl group. The ketone **1g** was readily obtained from 5-pentanol[17] via bromination,[18], Gringnard reaction with acetaldehyde and chromic oxidation.[19]

To the suspension of grown cells of P. miso, racemic acetate **4g** was added and incubated for two days. Extraction of the broth and purification afforded (S)-**4g** of $[\alpha]_D^{26}$ -24.5° (c 1.63, C_6H_6) in a yield of 32%, accompanied by the formation of

ketone **1g**. The enantiomeric excess of recovered optically active **4g** was determined to be over 99% based on ^{1}H NMR obtained in the presence of a chiral NMR shift reagent [Eu(tfc)$_3$]. In this stage, the absolute configuration was estimated to be S in analogy with other compounds obtained by the same enzymatic hydrolysis.



Scheme 4

Thus, obtaining necessary chiral synthon in hand, next essential step is the conversion of the cyano group to the hydroxymethyl group without any loss of the optical purity. Reduction of (S)-**4g** with diisobutylaluminum hydride or lithium aluminum hydride suffered from partial elimination of hydrogen cyanide, and gave the desired product in poor yields. Then, we planned to reduce the cyano group after derivation to carboxylate. In this case, acidic hydrolysis could not be employed because the substrate has a double bond which is sensitive to acidic conditions. To carry out the hydrolysis of cyano group under basic conditions, the protecting group of the hydroxyl was replaced from acetyl to tetrahydropyranyl. Deacetylation was successfully achieved by refluxing **4g** in ethanol in the presence of catalytic amount of p-toluenesulfonic acid. Hydrolysis of **8** with potassium hydroxide in aqueous ethanol followed by methylation and reduction with lithium aluminum hydride gave the desired olefinic diol **10** in 36% yield from **4g**. The final step is the oxidation of the terminal double bond to the methyl ketone. Oxidation with palladium (II) chloride and molecular oxygen was rather troublesome in isolation of the product, because it is volatile. Accordingly we employed a sequence of oxymercuration-demercuration and oxidation of the resulting sec-alcohol. Mercuric acetate was reacted after acetonide formation of diol group. Demercuration via ordinary process and oxidation of the resulting alcohol afforded protected ketone. As frontalin is volatile, deacetalization was carried out in pentane and concentrated hydrochloric acid. Frontalin thus obtained exhibited $[\alpha]_D^{26}$ -50.4° (c 1.19, Et_2O) indicating that it is the physiologically active natural (S)-enantiomer. Although this value is a little lower compared to the highest value $[\alpha]_D^{23}$ -54.4° (c 1.33, Et_2O) reported by Ohrui and Emoto,[5] the enantio excess of **6** thus obtained was confirmed to be over 99% by 400 MHz ^{1}H NMR analysis in the presence of chiral NMR shift reagent Eu(hfc)$_3$.†

†Eu(hfc)$_3$: Tris[3-heptafluoropropylhydroxymethylene)-(+)-camphorato]europium (III)

EXPERIMENTAL

Boiling points are uncorrected. Optical rotations were recorded on a JASCO DIP-360 Digital polarimeter. IR spectra were recorded in neat on a JASCO A-202 spectrophotometer, unless otherwise stated. ^{1}H NMR spectra were measured on JEOL JNM-GX 400 (400 MHz), JNM-FX 90A (90 MHz) and Varian EM-390 (90 MHz) NMR spectrometer using tetramethylsilane as the internal standard. Mass spectra were obtained on a Hitachi M-80 spectrometer. TLC was performed on Merck Kieselgel 60 F_{254} Art 5715 for analytical and Wako Gel B-5F for preparative scale. Column chromatography was effected using silica gel 60 KO7O-WH (70-230 mesh) of Katayama Kagaku Co.

1-Cyano-1-methylpropyl acetate (**4a**). To a soln of $Na_2S_2O_5$ (27 g, 0.14 mol) in water (70 ml) was added dropwise 2-butanone (**1a**, 10 g, 0.14 mol) stirring in an ice-water bath. Water is added to dissolve the resulting precipitates and was added a soln of KCN (25 g, 0.39 mol) in water (60 ml) stirring at 5°C. After the addition was complete, the pH of the reaction mixture was adjusted to 5.0 with conc HCl, extracted with CH_2Cl_2 (100 ml x 4), dried over Na_2SO_4 and concentrated in vacuo. The trace of water was removed as an azeotropic mixture with benzene. The resulting crude cyanohydrin was dissolved in a mixture of pyridine (50 ml) and Ac_2O (20 ml), and the soln was stirred overnight at room temp. The reaction mixture was poured into a mixture of ice and 2N HCl, extracted with EtOAc (100 ml x 4). The organic layer was washed with water, sat $NaHCO_3$ soln, brine and dried over Na_2SO_4. Evaporation of the solvent, followed by distillation in vacuo gave **4a** as a colorless oil (76%). B.p. 78~81°C/20 mmHg, vmax 2980, 2950, 1750, 1460, 1370, 1230, 1160, 1010, 945, 855 cm^{-1}; δ (CCl_4) 1.06 (t, 3H, J=7.2 Hz), 1.66 (s, 3H), 2.03 (s, 3H), 1.80~2.15 (m, 2H); MS (m/z, rel intensity) 142 [16 $(M+1)^+$], 112 (7), 99 (5), 98 (5), 82 (13), 81 (17), 71 (10), 70 (12), 59 (8), 56 (10), 43 (100).

The following cyanohydrin acetates were prepared according to the same procedure.

1-Cyano-1-methylbutyl acetate (**4b**). B.p. 71~73°C/4 mmHg, vmax 2960, 2880, 1750, 1460, 1370, 1230, 1160, 1125, 1110, 960, 930, 840 cm^{-1}; δ (CCl_4) 0.98 (t, 3H, J=6.8 Hz), 1.68 (s, 3H), 1.33~2.10 (m, 4H), 2.03 (s, 3H); MS (m/z, rel intensity) 156 [42, $(M+1)^+$], 129 (7), 112 (11), 96 (8), 95 (20), 94 (19), 71 (13), 68 (16), 43 (100).

1-Cyano-1-methylheptyl acetate (**4c**). B.p. 94~99°C/3 mmHg, vmax 2950, 1750, 1460, 1370, 1225, 1170, 1130, 1065, 1045, 1010, 945, 720 cm^{-1}; δ (CCl_4) 0.89 (t, 3H, J=6.8 Hz), 1.11~1.59 (m, 8H), 1.67 (s, 3H), 2.03 (s, 3H), 2.31 (t, 2H, J=7 Hz); MS (m/z, rel intensity) 198 [100 $(M+1)^+$], 171 (33), 152 (26), 138 (34), 129 (26), 95 (60), 83 (21), 68 (15), 55 (15), 43 (96).

1-Cyano-1,2-dimethylpropyl acetate (**4e**). B.p. 61~64°C/2.3 mmHg, vmax 2960, 1750, 1460, 1370, 1230, 1150, 1130, 1070, 1040, 1010, 945 cm^{-1}; δ (CCl_4) 1.07 (dd, 6H, J=3.0, 6.5 Hz), 1.64 (s, 3H), 2.04 (s, 3H), 1.96~2.36 (m, 1H); MS (m/z, rel intensity) 156 [15, $(M+1)^+$], 129 (10), 113 (53), 96 (25), 95 (41), 71 (79), 43 (100).

1-Cyano-1-methyldecyl acetate (**4d**). To a suspension of ZnI_2 (100 mg) in dry CH_2Cl_2 (6 ml) were added 2-undecanone (2.50 g, 14.7 mmol) and TMSCN (2.10 ml, 16.7 mmol), and the mixture was heated under reflux for 3 hr. The solvent was removed in vacuo. The residue was dissolved in Ac_2O (1 ml) and kept stirring for 6 hr after the addition of $FeCl_3$ (360 mg, 2.2 mmol).[20] The resulting mixture was extracted with hexane and the organic layer was washed sequentially with water, sat $NaHCO_3$ soln, brine, and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (hexane-EtOAc=5:1) to give **4d** (2.6 g, 75%) as a colorless oil, vmax 2910, 2840, 1750, 1450, 1360, 1225, 1165, 1120 cm^{-1}; δ (CCl_4) 0.98 (t, 3H, J=6.8 Hz), 1.10~1.60 (m, 16H), 1.73 (s, 3H), 2.08 (s, 3H); MS (m/z, rel intensity) 240 [4, $(M+1)^+$], 196 (17), 150 (12), 136 (18), 109 (21), 95 (30), 83 (22), 43 (100).

1-Cyano-1-methyl-5-hexenyl acetate (**4g**). To a soln of 6-hepten-2-one (**1g**, b.p. 146-149°C, 10 g, 89 mmol) and ZnI_2 (400 mg, 1.3 mmol) in dry CH_2Cl_2 (50 ml) was added TMSCN (14 ml, 110 mmol) stirring under Ar. After stirring under reflux for 10 min, the solvent and excess TMSCN were evaporated in vacuo. The residue was dissolved in MeOH (100 ml) and heated under reflux with a catalytic amount of pyridinium tosylate for 6 hr. MeOH was evaporated in vacuo and the residual oil was dissolved in a mixture of C_5H_5N (40 ml) and Ac_2O (30 ml) cooling in an ice-water bath. After the addition of a catalytic amount of 4-(N,N-dimethylamino)pyridine, the mixture was kept stirring overnight at room temp. Then, the contents of the flask was poured into a mixture of ice and 360 ml of 2N HCl, and extracted with EtOAc (100 ml x 5). The combined organic layer was washed with sat $NaHCO_3$ soln and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane-EtOAc=15:1) to give **4g** (10.2 g, 63% from **1g**) as a colorless oil, vmax 3090, 2925, 1750, 1640, 1440, 1370, 1230, 1180, 1110, 1030, 910 cm^{-1}; δ (CCl_4) 1.45~2.25 (m, 6H), 2.01 (s, 3H), 2.36 (s, 3H), 4.89~5.12 (m, 2H), 5.51~5.98 (m, 1H). MS (m/z, rel intensity) 182 [100, $(M+1)^+$], 164 (15), 155 (14), 138 (12), 122 (48), 121 (19), 120 (17), 113 (36), 111 (17), 106 (17), 95 (32), 94 (17), 54 (56), 43 (81).

1-Cyano-1,3-dimethylbutyl acetate (**4f**). In the same manner as described for **4g**, **4f** was prepared from **1f** (82%), vmax 2940, 2880, 1755, 1470, 1370, 1270, 1200, 1160, 1060, 1045, 1010, 945 cm^{-1}; δ (CCl_4) 1.01 (d, 6H, J=5.4 Hz), 1.70 (s, 3H), 2.05 (s, 3H), 1.50~2.12 (m, 3H); MS (m/z, rel intensity) 170 [23, $(M+1)^+$], 127 (25), 126 (36), 113 (40), 112 (19), 109 (24), 108 (26), 94 (63), 82 (25), 71 (19), 68 (20), 43 (100).

Incubation of (±)-cyanohydrin acetates (**4**) with Pichia miso: General procedure. Pichia miso IAM 4682 was grown in 50 ml of a sterilized medium consisted of glucose (1%), yeast extract (0.5%), peptone (0.7%) and K_2HPO_4 (0.5%) for 2 days at 30°C. The pH of the medium was initially adjusted to 7.2. (±)-1-Cyano-1-alkyl or alkenyl acetate (**4**, 0.15 ml) was added to the suspension of grown cells, and the incubation was continued for periods specified in

Table 1. The broth was extracted with EtOAc (50 ml x 3). The combined organic layer was dried over Na_2SO_4. The solvent was evaporated in vacuo to result a mixture of (S)-**4** and the corresponding ketone **1**. The mixture was purified by silica gel flash chromatography (hexane-EtOAc=9:1) to afford pure (S)-**4**. IR, ^1H NMR and mass spectra were identical with those of racemic compound. The enantiomeric excess was determined based on ^1H NMR spectrum obtained in the presence of 0.5~0.6 equivalent of $Eu(tfc)_3$: Two signals due to acetyl group were observed for racemic **4** corresponding to two enantiomers, as summarized below. The sole or stronger signals for optically active ones are underlined. The equivalents of added shift reagent is shown in the parentheses. **4a**: 2.53, 2.57 (0.5); **4b**: 2,51, 2.55 (0.5); **4c** 2.24, 2.28 (0.5); **4d**: 2.57, 2.65 (0.6); **4e**: 2.52, 2.59 (0.5); **4f**: 2.40, 2.47 (0.6); **4g**: 2.079, 2.159 (0.6).

(S)-2-Hydroxy-2-methylpentanoic acid (**5**). A mixture of (-)-**4b** (199 mg, 1.29 mmol) and conc HCl (4 ml) was heated at 100°C for 24 hr. After the addition of $(NH_4)_2SO_4$, the reaction mixture was extracted with Et_2O and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was purified by preparative TLC (hexane-acetone=1:1) on silica gel to afford **5** as a colorless oil (21 mg, 13%), $[\alpha]_D^{26}$ +9.53° (c 2.12, $CHCl_3$); νmax 3450, 2960, 1710, 1450, 1230, 1150, 1050 cm^{-1}; δ ($CDCl_3$) 0.89 (t, 3H, J=6.6 Hz), 1.42 (s, 3H), 1.35~1.84 (m, 4H), 6.87 (bs, 2H).

(S)-1-Cyano-1-methyl-5-hexenol tetrahydropyranyl ether (**8**). A soln of **4g** (1.13 g, 6.23 mmol) and catalytic amount of p-TsOH in EtOH (25 ml) was heated under reflux overnight. Then the reaction mixture was concentrated in vacuo. The residual oil was filtered through silica gel to give crude 1-cyano-1-methyl-5-hexenol (652 mg). νmax 3450, 2990, 2950, 2880, 1640, 1455, 1380, 1125, 910 cm^{-1}; δ (CCl_4) 1.16~1.84 (m, 4H), 1.19 (s, 3H), 1.94~2.25 (m, 2H), 3.95 (bs, 1H), 4.85~5.07 (m, 2H), 5.52~5.97 (m, 1H). This crude alcohol was used to the next reaction without further purification.

A catalytic amount of p-TsOH was added to a soln of crude cyanohydrin (652 mg) and dihydropyran (5 ml) in CH_2Cl_2 (25 ml) with stirring in an ice-cooled bath. The stirring was continued for 5 hr at room temp. The reaction was quenched by the addition of 1N NaOH soln at 0°C. The mixture was extracted with CH_2Cl_2 (10 ml x 4), and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residual oil was purified by flash column chromatography (hexane-EtOAc=10:1) to give **8** (913 mg, 66% from **4g**). νmax 2940, 2870, 1730, 1640, 1450, 1440, 1375, 1200, 1125, 1070, 1020, 965, 910 cm^{-1}; δ (CCl_4) 1.24~2.29 (m, 12H), 1.51 (s, 1.5H), 1.55 (s, 1.5H), 3.34~3.63 (m, 1H), 3.67~3.99 (m, 1H), 4.86~5.07 (m, 3H), 5.18~6.06 (m, 1H); MS (m/z, rel intensity) 138 (3.5), 122 (42), 101 (17), 95 (26), 85 (100), 84 (14), 67 (13), 56 (17), 55 (17), 43 (20).

(S)-Methyl 2-methyl-2-hydroxy-6-heptenoate (**9**). To a soln of **8** (913 mg, 4.09 mmol) in EtOH (20 ml) was added an aq soln of KOH (20 ml), and the mixture was heated under reflux for 40 hr. Then, the pH of the soln was adjusted to 1 by adding 2N HCl at 0°C and the soln was kept stirring for 10 min. The mixture was extracted with Et_2O (10 ml x 6) after the addition of $(NH_4)_2SO_4$. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was dissolved in Et_2O (2 ml) and treated with an excess amount of CH_2N_2. The solvent was evaporated in vacuo and the resulting oil was purified by flash column chromatography on silica gel (hexane-EtOAc=20:1) to give **9** [434 mg, 62% based on (S)-**8**] as a colorless oil. $[\alpha]_D^{25}$ +16° (c 1.2, $CHCl_3$); νmax 3600, 2940, 2860, 2220, 1740, 1580, 1555, 1365 cm^{-1}; δ (CCl_4) 1.12~1.73 (m, 4H), 1.30 (s, 3H), 1.89~2.12 (m, 2H), 2.89 (bs, 1H), 3.71 (s, 3H), 4.80~5.02 (m, 2H), 5.48~5.93 (m, 1H); MS (m/z, rel intensity): 155 (1), 154 (3.2), 113 (71), 104 (25), 103 (12), 95 (50), 94 (16), 71 (17), 58 (12), 55 (31), 54 (34), 43 (100), 41 (22), 39 (17).

(S)-2-Methyl-6-heptene-1,2-diol (**10**). To a soln of **9** (20 mg, 0.12 mmol) in dry THF (0.5 ml) was added $LiAlH_4$ (10 mg, 0.26 mmol) stirring in an ice-water bath, and the soln was kept stirring for 1 hr at room temp. The reaction was quenched by dilution with Et_2O followed by the addition of $Na_2SO_4 \cdot H_2O$ at 0°C. The mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The residual oil was purified by flash column chromatography on silica gel (hexane-EtOAc-MeOH=60:30:1) to give **10** (14.7 mg, 88%) as a colorless oil. $[\alpha]_D^{25}$ -2.6° (c 1.4, $CHCl_3$), νmax 3390, 2940, 1640, 1460, 1375, 1130, 1045, 905 cm^{-1}; δ (CCl_4): 1.06 (s, 3H), 1.11~1.69 (m, 4H), 1.89~2.21 (m, 2H), 2.97 (bs, 2H), 3.29 (s, 2H), 4.83~5.04 (m, 2H), 5.51~5.96 (m, 1H); MS (m/z, rel intensity) 113 (8), 95 (6), 75 (14), 59 (17), 57 (13), 55 (16), 45 (17), 43 (100), 41 (23), 39 (18).

(S)-Frontalin (**6**). A soln of **10** (167 mg, 1.16 mmol) and 2,2-dimethoxypropane (240 mg, 2.31 mmol) in dry acetone (2 ml) was stirred for 10 min at room temp. The mixture was concentrated in vacuo and extracted with Et_2O (10 ml x 4) after the addition of sat $NaHCO_3$ soln. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give crude (S)-2-methyl-6-heptene-1,2-diol acetonide (187 mg). νmax 2980, 2940, 2860, 1640, 1450, 1370, 1245, 1210, 1055, 910 cm^{-1}; δ (CCl_4) 1.08~1.66 (m, 4H), 1.16 (s, 3H), 1.26 (s, 6H), 1.85~2.20 (m, 2H), 3.52 (d, 1H, J=7.2 Hz), 3.63 (d, 1H, J=7.2 Hz), 4.81~5.02 (m, 2H), 5.49~5.96 (m, 1H). This acetonide was subjected to the next step without further purification.

To a soln of $Hg(OAc)_2$ (330 mg, 1.03 mmol) in water (1 ml) was added THF (1 ml) stirring at room temp. When the soln turned yellow, crude acetonide obtained above (187 mg) was added dropwise, and the stirring was continued for 10 min. Then, 3N NaOH soln (1 ml) and 0.5M soln of $NaBH_4$ in 3N NaOH soln (1 ml) were sequentially added. The mixture was filtered through a pad of Celite, the filtrate being extracted with Et_2O (10 ml x 5). The combined organic layer was concentrated in vacuo to give crude 1,2-O-isopropylidene-2-methylheptane-1,2,6-triol (202 mg), which was subjected to the next step without further purification. νmax 3400, 2950, 2920, 2860, 1450, 1365, 1240, 1200, 1110, 1055, 840, 800 cm^{-1}; δ (CCl_4) 0.85~1.77 (m, 7H), 1.11 (d, 3H, J=5.4 Hz), 1.18 (s, 3H), 1.27 (s, 6H),

3.53 (d, 1H, J=8.1 Hz), 3.65 (d, 1H, J=8.1 Hz), 3.42~3.89 (m, 1H).

To a suspension of pyridinium chlorochromate[21] (450 mg) and powdered Molecular Sieves 3A (350 mg) in CH_2Cl_2 (3 ml) was added dropwise a soln of crude acetonide alcohol (202 mg) in CH_2Cl_2 (1 ml) stirring in an ice-water bath. Then, Florisil (1.75 g) and dry Et_2O (20 ml) was added to the reaction mixture. The mixture was filtered through pads of Celite and Florisil, and the filtrate was concentrated *in vacuo* to give crude (S)-6,7-O-isopropylidene-6,7-dihydroxy-6-methyl-2-heptanone (189 mg), which was subjected to the next step without further purification. νmax 2980, 2930, 2860, 1710, 1450, 1370, 1240, 1210, 1110, 1050, 980, 900, 860, 800 cm^{-1}; δ (CCl_4) 1.07~1.84 (m, 4H), 1.19 (s, 3H), 1.27 (s, 6H), 2.01 (s, 3H), 2.36 (t, 2H, J=5.9 Hz), 3.54 (d, 1H, J=8.1 Hz), 3.65 (d, 1H, J=8.1 Hz).

To a soln of crude ketone obtained above (189 mg) in pentane (1 ml) was added 10 drops of 2N HCl, and the soln was kept stirring for 1 hr at room temp. Then, the reaction mixture was extracted with pentane after the addition of a small amount of NaCl. The combined organic layer was washed with sat $NaHCO_3$ soln and dried over Na_2SO_4. The solvent was removed under atmospheric pressure and the residual oil was purified by distillation using Kugelrohl apparatus to yield (S)-frontalin (**6**) (80 mg, 48% from **10**). B.p. 100°C/105 mmHg, $[\alpha]_D^{26}$ -50.4° (c 1.19, Et_2O); ν (CCl_4 soln) 2980, 2940, 2880, 1450, 1390, 1380, 1260, 1240, 1200, 1170, 1120, 1060, 1030, 930, 890, 865, 845 cm^{-1}; δ ($CDCl_3$) 1.34 (s, 3H), 1.44 (s, 3H), 1.26~2.02 (m, 6H), 3.45 (d, 1H, J=6.3 Hz), 3.92 (d, 1H, J=6.3 Hz); MS (m/z, rel intensity) 144 [11, $(M+2)^+$], 143 [100, $(M+1)^+$], 142 (46, M^+), 125 (34), 114 (12), 112 (26), 100 (57), 72 (61), 71 (21), 43 (64).

The enantiomeric excess of the resulting (S)-frontalin was determined by ^1H NMR using $Eu(hfc)_3$. Measurement of ^1H NMR of racemic frontalin in the presence of 1 equivalent of the chiral shift reagent resulted in the separation of the signal due to C(1)-methyl group into δ 2.70 and 2.77 ppm. On the other hand, only the signal in the lower field was observed in the spectrum of optically active one. Thus, the product can be concluded to be enantiomerically pure within the error of 400 MHz NMR.

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