Enantioselective Synthesis of (−)-Frontalin†

Suk-Ku Kang*, Ho-Sik Rho, and Eun-Young Namkoong

Department of Chemistry, Sung Kyun Kwan University, Natural Science Campus, Suwon 440-746, Korea

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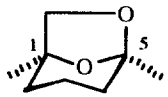
(*S*)-(−)-Frontalin **1** is known to be the aggregation pheromone of the southern pine beetle *Dendroctonus frontalins*.[1] The biologically active form of this 1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane compound is the (1*S*, 5*R*)-enantiomer, **1** (Figure 1).[2] Since its antipode has been reported to be inactive, enantioselective syntheses of frontalin are of great interest. A number of enantioselective syntheses of both (+)- and (−)-frontalin have been reported.[3]

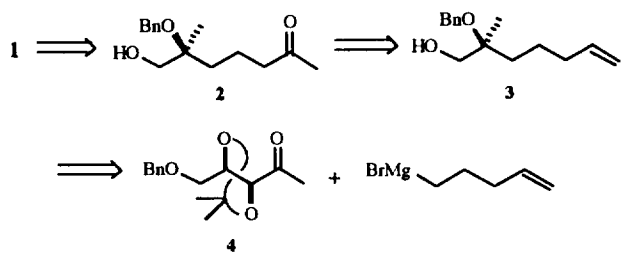


(1*S*, 5*R*)- **1**

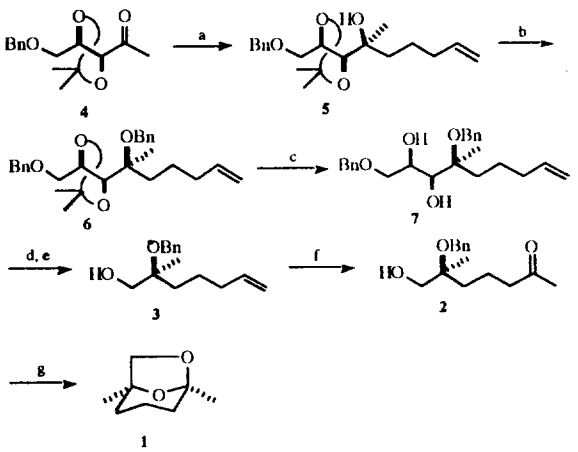
Figure 1.

Although frontalin contains two asymmetric centers, only the stereoselective formation of the (1*S*) center needs to be considered since the correct configuration at C-5 is dictated by this carbon center during the formation of the bicyclic structure. We report here enantioselective synthesis based on asymmetric synthesis *i.e.*. "self-reproduction of chirality" method. The retrosynthetic analysis is shown in Scheme 1. Since (−)-frontalin **1** can be viewed as being formed by internal acetalization of the dihydroxyketone, benzyl protected compound **2** can be the intermediate. Methyl ketone functionality in **2** can be synthesized from terminal olefin **3** by Wacker oxidation. The compound **3** can be obtained by chelation-controlled addition of Grignard reagent to the keto acetonide **4** followed by deprotection, oxidative cleavage, and reduction. The compound **4** can be derived from D-tartrate (Scheme 1).

Chelation-controlled addition of pentenylmagnesium bromie to the keto acetonide **4**[4] at −78 ℃ in THF afforded the alcohol **5**[5] in 92% yield. Protection of the alcohol **5** with benzyl bromide provided the benzyl ether **6** in 95% yield. Deprotection of the acetonide moiety with aquous HCl yielded the diol **7** in 75% yield. Oxidative cleavage of the diol with $Pb(OAc)_4$ in CH_2Cl_2 followed by the $NaBH_4$ reduction afforded the alcohol **3** in 70% overall yield. Palladium-catalyzed Wacker oxidation[6] of **3** with $PdCl_2$ (10 mol%) with benzoquinone as oxidant afforded the penultimate product **2** in 89% yield. In our hands, Wacker oxidation[7] of **3** with $PdCl_2$ (cat), CuCl, O_2 in DMF/H_2O (7 : 1) system did not work. Finally, debenzylation with H_2 at atmosperic pressure afforded the target bicyclic compound **1**, $[\alpha]_D^{25} = -44.2$ (*c* 0.25, Et_2O), [lit.[3q] $[\alpha]_D^{20}$ −45 (Et_2O)] in 80% yield (Scheme 2). The spectral and physical data of **1** thus synthesized were identical with the data reported in the literature.[3]



Scheme 1.



Reagents and Conditions: (a) $H_2C=CH(CH_2)_3MgBr$, THF, −78 ℃, 4 h. (b) NaH, $PhCH_2Br$, TBAI (cat.), 10 min. (c) 10% HCl, THF, rt, 24 h. (d) $Pb(OAc)_4$, CH_2Cl_2, rt, 30 min. (e) $NaBH_4$, EtOH, rt, 20 min. (f) $PdCl_2$, benzoquinone, 5% aqueous THF, rt, 2 h. (g) H_2, 10% Pd/C, 1 atm, MeOH, rt, 3 h.

Scheme 2.

Experimental

(6*S*,7*S*,8*R*)-9-Benzyloxy-7,8-isopropylidenedioxy-6-methyl-1-nonene-6-ol (5). To a stirred solution of acetonide ketone **4** (300 mg, 1.2 mmol) in dry THF (5 mL) at −78 ℃ was added pentenylmagnesium bromide (1.2 mL, 2.4 mmol, 2 M solution in THF) and stirred for 4 h at −78 ℃. The reaction mixture was quenched with saturated NH_4 Cl solution (1 mL). THF was evaporated and the residue was extracted with diethyl ether (30 mL). The ether layer was dried over anhydrous magnesium sulfate and evaporated *in vacuo*. The crude product was separated by SiO_2 column chromatography (EtOAc./hexanes 1 : 3 R_f=0.57) to afforded **5** (368 mg, 92%). TLC; SiO_2, EtOAc/hexanes 1 : 3, R_f=0.57. $[\alpha]_D^{25} = +2.4$ (*c* 1.75, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 3H), 1.40 (m, 6H), 1.49-1.60 (m, 4H), 2.01 (m, 2H), 2.20 (bs, 1H), 3.50 (dd, 1H, *J*=10.1, 3.5 Hz), 3.75 (d, 1H, *J*=8.0 Hz), 4.18 (m, 1H), 4.56 (s, 2H), 5.01 (m, 2H), 5.75 (m, 1H), 7.32 (m, 5H). IR (neat) 3550, 3080, 2910, 1620 cm^{-1}. MS (m/e) 334 (M^+), 243, 113, 107, 91 (base peak), 72.

(6*S*,7*S*,8*R*)-9,6-Dibenzyloxy-7,8-isopropylidenedioxy-6-methyl-1-nonene (6). To a stirred solution of **5** (280 mg, 0.84 mmol) in DMF (3 mL) under N_2 were added NaH (80 mg, 3.36 mmol) and tetrabutylammonium iodine (cat.) and the reaction mixture was stirred for 10 min. To this reaction mixture was added benzylbromide (574 mg, 3.36 mmol) and then stirred at reflux for 30 min. The solution

was cooled and then extracted with diethyl ether (30 mL). The ether layer was dried over anhydrous magnesium sulfate and evaporated *in vacuo*. The crude product was separated by SiO_2 column chromatography (EtOAc./hexanes 1 : 3 R_f=0.75) to afforded **6** (338 mg, 95%). TLC; SiO_2, EtOAc/hexanes 1 : 3, R_f=0.75. $[\alpha]_D^{25}$= +10.8 (*c* 0.75, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 1.10 (s, 3H), 1.42 (m, 6H), 1.49-1.60 (m, 4H), 2.04 (m, 2H), 3.52 (dd, 1H, *J*=10.2, 8.3 Hz), 3.60 (dd, 1H, *J*=10.1, 3.4 Hz), 3.95 (d, 1H, *J*=7.9 Hz), 4.30 (m, 1H), 4.48 (s, 2H), 4.60 (s, 2H), 5.02 (m, 2H), 5.78 (m, 1H), 7.35 (m, 10H). IR (neat) 3090, 2905, 1625 cm $^{-1}$. MS (m/e) 424 (M^+), 221, 203, 107, 91 (base peak).

(6*S*,7*S*,8*R*)-9,6-Dibenzyloxy-6-methyl-1-nonene-7,8-diol (7). To a stirred solution of **6** (300 mg, 0.70 mmol) in THF (3 mL) was added 10% aqueous HCl (0.4 mL) and then stired at room temperature for 24 h. To the reaction mixture was added saturated sodium bicarbonate solution (1 mL) and stirred for 20 min, and then extracted with diethyl ether (40 mL). The ether layer was dried over anhydrous magnesium sulfate and evaporated *in vacuo*. The crude product was separated by SiO_2 column chromatography (EtOAc/hexanes 1 : 3 R_f=0.30) to afforded **7** (201 mg, 75%). TLC; SiO_2, EtOAc/hexanes 1 : 3, R_f=0.30. $[\alpha]_D^{25}$= −7.6 (*c* 0.41, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) δ 1.10 (s, 3H), 1.49-1.60 (m, 4H), 2.10 (bs, 2H), 3.55 (m, 2H), 3.75 (d, 1H, *J*=8.0 Hz), 4.20 (m, 1H), 4.49 (s, 2H), 4.60 (s, 2H), 5.00 (m, 2H), 5.75 (m, 1H), 7.30 (m, 10H). IR (neat) 3500, 3050, 2930, 1640 cm $^{-1}$. MS (m/e) 384 (M^+), 181, 203, 107, 91 (base peak), 79.

(6*S*)-6-Benzyloxy-6-methyl-1-heptene-7-ol (3). To a stirred solution of **7** (400 mg, 1.04 mmol) in dry CH_2Cl_2 (2 mL) under N_2 was added $Pb(OAc)_4$ (922 mg, 2.08 mmol). After stirring for 30 min, the reaction mixture was filtered through celite pad and evaporated *in vacuo* to afforded the crude aldehyde. To a solution of sodium borohydride (118 mg, 3.12 mmol) in EtOH (3 mL) was added the crude aldehyde (243 mg, 1.04 mmol) and then the reaction mixture was stirred for 20 min. After quenching with saturated NH_4Cl, the reaction mixture was extracted with diethyl ether (30 mL). The ether layer was dried over anhydrous magnesium sulfate and evaporated *in vacuo*. The crude product was separated by SiO_2 column chromatography (EtOAc/hexanes 1 : 3 R_f=0.33) to afforded **3** (170 mg, 70%). TLC; SiO_2, EtOAc/hexanes 1 : 3, R_f=0.33. $[\alpha]_D^{25}$= −3.6 (*c* 1.00, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) δ 1.15 (s, 3H), 1.45-1.65 (m, 4H), 2.15 (m, 2H), 3.52 (s, 2H), 4.45 (s, 2H), 5.00 (m, 2H), 5.80 (m, 1H), 7.37 (m, 5H). IR (neat) 3520, 3060, 2980, 1630 cm^{-1}. MS (m/e) 234 (M^+), 203, 143, 107, 91 (base peak), 79, 55.

(6*S*)-7-Hydroxy-6-benzyloxy-6-methyl-2-heptanone (2). To a stirred solution of **3** (150 mg, 0.64 mmol) in 5% aqueous THF (2 mL) was added $PdCl_2$ (11.4 mg, 0.064 mmol) and benzoquinone (69.2 mg, 0.64 mmol). After stirring for 2 h at room temperature, the reaction mixture was filtered through Celite pad and evaporated *in vacuo*. The crude product was separated by SiO_2 column chromatography (EtOAc /hexanes 1 : 1 R_f=0.28) to afforded **2** (142 mg, 89%). TLC; SiO_2, EtOAc/hexanes 1 : 1, R_f=0.28. $[\alpha]_D^{25}$= −20 (*c* 0.25, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, 2H, *J*=7.1 Hz), 1.25 (s, 3H), 1.95 (m, 2H), 2.10 (s, 3H), 2.43 (t, 2H, *J*=6.7 Hz), 3.58 (s, 2H), 4.45 (s, 2H), 7.35 (m, 5H). IR (neat) 3510, 3065, 2985, 1710 cm^{-1}. MS (m/e) 250 (M^+), 159, 107, 91 (base peak), 77, 71.

(*S*)-Frontalin (1) : (*S*)-(−)-1,5-Dimethyl-6,8-dioxabicyclo[3,2,1]octane (1). To a stirred solution of **2** (100 mg, 0.40 mmol) in dry MeOH (2 mL) under H_2 was added $PdCl_2$ (40 mg, 10 mol%) and stirred for 3 h. The catalyst was removed by filtration and solvent was distilled through a short vigreux column at atmospheric pressure. The crude material was purified by distillation using Kugelrohr apparatus to yield (*S*)-frontalin **1** (45.4 mg, 0.32 mmol, 80%). TLC; SiO_2, EtOAc/hexanes 1 : 2, R_f=0.50. $[\alpha]_D^{25}$= −44.2 (*c* 0.25, Et_2O). ^1H NMR (200 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.43 (s, 3H), 1.15-2.10 (s, 6H), 3.48 (d, 1H, *J*=6.2 Hz), 3.95 (d, 1H, *J*=6.2 Hz).

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References

†This paper is dedicated to professor Woon Sun Ahn in honor of his retirement.

1. Kinzer, G. W.; Fentiman, A. F. Jr., Page, T. F. Jr.; Foltz, R. L.; Vite, J. P.; Pitman, G. B. *Nature* **1969**, *221*, 447.
2. Wood, D. L.; Browne, L. E.; Ewing, B.; Lindahl, K.; Bedard, W. D.; Tilaen, P. E.; Mori, K.; Pitman, G. B.; Hughes, P. K. *Science* **1976**, *192*, 896.
3. Review: (a) Mori, K. *Total Synhesis of Natural products*; Ap Simon, J. Ed., John Wiley & Son: New York 1992; Vol. 9 and Vol. 4. (b) Optical resolution: Mori, K. *Tetrahedron* **1975**, *31*, 13181. (c) Chiral building blocks: Ohrui, H.; Emoto, S. *Agric. Biol. Chem.* **1976**, *40*, 2267. (d) Kawana, M.; Emoto, S. *Tetrahdron Lett.* **1975**, 3395. (e) Jarosz, S.; Hicks, D. R.; Fraser-Reid, B. *J. Org. Chem.* **1982**, *47*, 935. (f) Trinh, M.-C.; Florent, J.-C.; Monneket, C. *Tetrahedron* **1988**, *44*, 6633. (g) Ohira, S.; Ishi, S.; Shinohara, K.; Nozaki, H. *Tetrahedron Lett.* **1990**, *31*, 1039. (h) Barner, R.; Hubscher, J. *Helv. Chim. Acta.* **1993**, *66*, 880. (i) Asymmetric synthesis (e.g. self-reproduction of chirality); Naef, R.; seebach, D. *Liebigs. Ann. Chem.* **1983**, 1930. (j) Mash, E. A.; Fryling, J. A. *J. Org. Chem.* **1991**, *56*, 1094. (k) Whell, J. K.; Buchanan, C. M. *J. Org. Chem.* **1986**, *51*, 5443. (l) Ohwa, M.; Eliel, E. L. *Chem. Lett.* **1987**, 41. (m) Sharpless asymmetric epoxidation: Meister, C.; Scharf, H.-D. *Liebigs. Ann. Chem.* **1983**, 913. (n) Lee, A. W. M. *J. Chem. Soc. Chem. Commun.* **1984**, 578. (o) Yadav, J. S.; Joshi, B. V.; Sahasrabudhe, A. B. J. *Synth. Commun.* **1985**, *15*, 797. (p) Hosokawa, T.; Makabe, Y.; Shinohara, T.; Murahashi, S-I. *Chem. Lett.* **1985**, 1529. (q) Baker's yeast mediated transformation: Fugant, C.; Grasselli, P.; Serri, S. *J. Chem. Soc Perkin Trans. I.* **1983**, 241. (r) Sato, T.; Maeno, H.; Noro, T.; Fujisawa, T. *Chem. Lett.* **1988**, 1739. (s) Biocatalytic kinetic resolution: Ohta, H.; Kimura, Y.; Sugano, Y.; Sugai, T. *Tetrahedron* **1989**, *45*, 5469. (t) Sharpless asymmetric dihydroxylation: Turgin, J. A.; Weige, L. O. *Tetrahedron Lett.* **1992**, *33*, 6563. (u) Santiago, B.; Soderquist, J. A. *J. Org. Chem.* **1992**, *57*, 5844.
4. The compound **4** was prepared from 4-*O*-benzyl-2,3-*O*-isopropylidene-D-threose (1) MeMgBr, THF, −78 ℃, 1 h (85%) (2) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 ℃, 2 h (80 %). For the preparation of 4-*O*-benzyl-2,3-*O*-isopropylidenedioxy-1,4-butanediol, see, Mukaiyama, T.; Suzki, K.; Ya-

mada, T.; Tabusa, F. *Tetrahedron* **1990**, *46*, 256.
5. The ratio was checked by 300 MHz ^{1}H NMR. The chemical shift for the methyl group of **5** thus prepared showed a doublet at δ 3.75 whereas the other isomer showed at δ 3.76 in 300 MHz ^{1}H NMR.
6. Miller, D. G.; Wayner, D. D. M. *J. Org. Chem.* **1990**, *55*, 2924.
7. Tsuji, J. *Synthesis* **1984**, 369.

Oxidation of $(PPh_3)_2(CO)_2Br_2Mo$(II) to $(Ph_3P=O)_2(O)_2Br_2Mo$(VI)

Hee-Sook Park, Hyo-Kyung Yu, June-Ho Jung, Young-Woong Kim, and Soon W. Lee*

Department of Chemistry, Sung Kyun Kwan University, Suwon, Kyung-Ki 440-746, Korea

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In the course of the reaction between *trans, cis, cis*-$(PPh_3)_2(CO)_2Br_2Mo$(II), **A**, and the primary amines in tetrahydrofuran (THF) under argon at room temperature, the continuous color change of **A** was observed. Compound **A** changed its color much more rapidly in air in various solvents even in the absence of the amines. This kind of air-sensitivity appeared to be both solvent- and temperature-dependent. We decided to investigate how the product was formed and to determine its molecular structure. Herein we report the preparation and structure of *cis, cis, trans*-$(Ph_3P=O)_2(O)_2Br_2Mo$(VI), **B**, which was formed by oxidation of **A**.

Experimental

Unless otherwise stated, all the reactions have been performed with standard Schlenk line and cannula techniques under an argon atmosphere. Air-sensitive solids were manipulated in a glove box filled with an argon gas. Glassware was either flame-dried or oven-dried. Benzene, diethyl ether, tetrahydrofuran (THF), and hydrocarbon solvents were stirred over sodium metal and distilled under vacuum. NMR solvents (C_6D_6 and $CDCl_3$) were freeze-pump-thaw degassed before use and stored over zeolite 4A under argon. Triphenylphosphine (PPh_3; Ph=C_6H_5) was purchased from Aldrich Co. and used as received. $(PPh_3)_2(CO)_2Br_2Mo$(II), **A**, was prepared by the literature method.[1]

^{1}H and ^{31}P NMR spectra were recorded with a Hitach 1100 60-MHz spectrometer and a Varian 200-MHz spectrometer with reference to tetramethylsilane and 85% H_3PO_4, respectively. IR spectra were recorded with a Nicolet 205 FTIR spectrophotometer. Melting points were measured with a Thomas Hoover capillary melting point apparatus without calibration.

Preparation of *cis, cis, trans*-$(Ph_3P=O)_2(O)_2Br_2Mo$ (VI), B. A blue slurry of **A** (0.3 g, 0.36 mmol) in 30 mL of THF was stirred for 4 h at room temperature or refluxed for 2 h in air to form a dark brown solution. The solution was filtered, concentrated, and layered by hexanes to give orange crystalline *cis, cis, trans*-$(Ph_3P=O)_2(O)_2Br_2Mo$(VI), **B**, (0.19 g, 63%). ^{1}H NMR ($CDCl_3$): δ 8.0-6.7 (m). ^{31}P{H} NMR ($CDCl_3$): δ 58.35. Mp (decomp): 271-273 ℃. IR (Nujol): 1155 (P=O), 1115, 1065, 1052, 972 (Mo=O, sym.), 894 (Mo=O, asym., sh), 853, 725 cm^{-1}.

X-ray Structure Determination. All X-ray data were collected with use of an Enraf-Nonius CAD4 automated diffractometer equipped with a Mo X-ray tube and a graphite crystal monochromator. Details on crystal and intensity data are given in Table 1. The orientation matrix and unit cell parameters were determined from 25 machine-centered reflections with $16<2\theta<24°$. Axial photographs were used to verify the unit cell choice. Intensities of three check reflections were monitored after every 1 h during data collection. Data were corrected for Lorentz and polarization effects. The intensity data were empirically corrected with ψ-scan data. All calculations were carried out on the personal computer with use of the SHELXS-86,[2] SHELXL-93[3] programs.

An orange crystal, shaped as a block, of approximate dimensions 0.2×0.2×0.3 mm, was used for crystal and intensity data collection. The unit cell parameters and systematic absences, $0k0$ ($k=2n+1$), $00l$ ($l=2n+1$), and $h0l$ ($l=2n+1$), unambiguously indicated $P2_1/c$ as the space group. The structure was solved by direct methods. All non-hydrogen atoms were refined anisotropically and the phenyl rings were treated as rigid groups. All hydrogen atoms were positioned geometrically and refined using a riding model. The selected bond distances and bond angles are shown in Table 2; final atomic positional parameters for non-hydrogen atoms, anisotropic thermal parameters for non-hydrogen atoms, hydrogen atom coordinates, full bond distances and bond angles, and tables of observed and calculated structure factors are available as supplementary materials.

Table 1. Crystallographic Data and Summary of Data Collection and Structure Refinement

formula	$C_{36}H_{30}O_4P_2Br_2Mo$	F(000)	1680
fw	844.30	no. of	2907
crystal system	monoclinic	unique data	
space group	$P2_1/c$	no. of reflns	2708
a, Å	19.097(3)	used, $I>2\sigma(I)$	
b, Å	9.973(3)	no. of params	340
c, Å	19.201(6)	Z	4
β, deg	111.32(2)	scan range	$3<2\theta<50°$
V, Å^3	3407(2)	scan type	ω-2θ
d_{calc}, g cm^{-3}	1.646	GOF	1.124
μ, mm^{-1}	2.863	R	0.0536
Max. in Δρ (e A^{3-})	0.61	wR_2[a]	0.1226

[a] $wR_2=\{\Sigma[w(F_o^2-F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$

Results and Discussion

Formation of B. A blue complex, *trans, cis, cis*-$(PPh_3)_2(CO)_2Br_2Mo$(II), **A**, was gradually air-oxidized to form a known orange complex *cis, cis, trans*-$(Ph_3P=O)_2(O)_2Br_2Mo$(VI), **B**, in THF for 4 h at room temperature (Eq. 1). This

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