Pheromone Synthesis, CLXXXVIII[◇]

A New Synthesis of (−)-Frontalin, the Bark Beetle Pheromone

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(−)-Frontalin [(1*S*,5*R*)-1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane (**1**)] was synthesized from ethyl 2-oxocyclopentane-1-carboxylate (**2**) as the starting material. Baker's yeast was used for the asymmetric reduction of **2** to **3**. The *S* configuration at C-1 of **1** was generated by diastereoselective methylation of the dianion derived from **3** to give **4**. The present process furnished about 10 g of **1** with enantiomeric purity of 89.1% e.e.

(−)-Frontalin [(1*S*,5*R*)-1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane (**1**), Scheme 1] is the active component of the aggregation pheromone of the southern pine beetle (*Dendroctonus frontalis*), the western pine beetle (*Dendroctonus brevicomis*) and the Douglas-fir beetle (*Dendroctonus pseudotsugae*)[1][2][3]. It may also show biological activity in elephants, because the temporal gland secretion during the condition of musth in the male Asian elephant (*Elephas maximus*) contains frontalin[4]. Mori's 1975 synthesis of the enantiomers of frontalin[5] enabled their bioassay, and only (1*S*,5*R*)-**1** was bioactive as the pheromone component of the western pine beetle[6]. The enantiomeric purity of (1*S*,5*R*)-frontalin (**1**) isolated from the southern pine beetle was 70% e.e. by NMR measurement in the presence of a chiral shift reagent[7]. Since Mori's first enantioselective synthesis of **1** in 1975[5], 18 additional syntheses of the enantiomers of **1** were reported prior to 1990[8]. Even after 1990, 15 different syntheses of **1** were executed by (i) employing enantiomerically pure building blocks such as D-lactose[9], (*S*)-lactic acid[10], (2*S*,3*S*,5*S*)-2,3-epoxy-3-methyl-5-trimethylsilylcyclohexanone[11], and (*S*)-2-hydroxyparaconic acid[12], or (ii) employing chiral auxiliaries[13][14] or chiral reagents[15][16] and also by the Sharpless asymmetric dihydroxylation[17][18][19], or (iii) enzymatic methods using lipases[20][21][22] or bacterial epoxide hydrolases[23].

Scheme 1. Structures of the male-produced pheromone components of *Dendroctonus jeffreyi*

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

(1*R*,5*S*,7*R*)-(+)-*exo*-Brevicomin

Recently, in 1996, Seybold identified (−)-frontalin (**1**, 76% e.e.) and (+)-*exo*-brevicomin (> 98% e.e.) as the pheromone components of the male Jeffrey pine beetle (*Dendroctonus jeffreyi*), an aggressive pest of Jeffrey pine (*Pinus jeffreyi*) in the U.S.A. This beetle kills large amounts of standing timber each year[24]. About 1 g of (+)-*exo*-brevicomin and about 10 g of (−)-frontalin were required for a field test[24]. There was no problem to prepare about 1 g of (+)-*exo*-brevicomin. Preparation of about 10 g of (−)-frontalin, however, was problematic, because most of the existing 34 syntheses were just small-scale preparations of academic interest. We eventually could prepare a multigram quantity of (−)-frontalin by the method detailed below in this paper.

Scheme 2 summarizes the present synthesis of (−)-frontalin. Asymmetric reduction of ethyl 2-oxocyclopentane-1-carboxylate (**2**) was first reported in 1976 by Deol et al.[25], and then by others[26][27][28][29][30] to give (1*R*,2*S*)-**3**. The known diastereoselective methylation[31][32] of the dianion derived from **3** and lithium diisopropylamide (LDA) gives (1*R*,2*S*)-**4**, establishing the *S* configuration at C-1 of **1**. The oxygen function at C-1 of **1** can be inserted by the Baeyer-Villiger oxidation of (*R*)-**5** to give (*S*)-**6**. This concept is similar to that employed in Fujisawa's 1988 synthesis[28], and seems to be suitable for our purpose of a multigram preparation of (1*S*,5*R*)-**1**.

The first step of our synthesis was the microbial asymmetric reduction of **2**. Although a microorganism (*Klebsiella pnemoniae* IFO 3319) other than baker's yeast is known to be a good catalyst to achieve the desired conversion[33], we preferred the conventional and more convenient baker's yeast, and obtained (1*R*,2*S*)-**3** in 52% yield with 97.7% e.e. and 99.0% d.e. as analyzed by GC on a chiral stationary phase [cf. (1*R*,2*S*)-**3** reported in ref.[28]: 89% e.e. and 94% d.e.]. Methylation of the dianion derived from (1*R*,2*S*)-**3** and LDA in THF gave (1*R*,2*S*)-**4** with diastereomeric purity of 84−87% d.e. Careful fractional distillation of the crude **4**, prepared from 60.0 g of **3**, yielded a fraction (48.0

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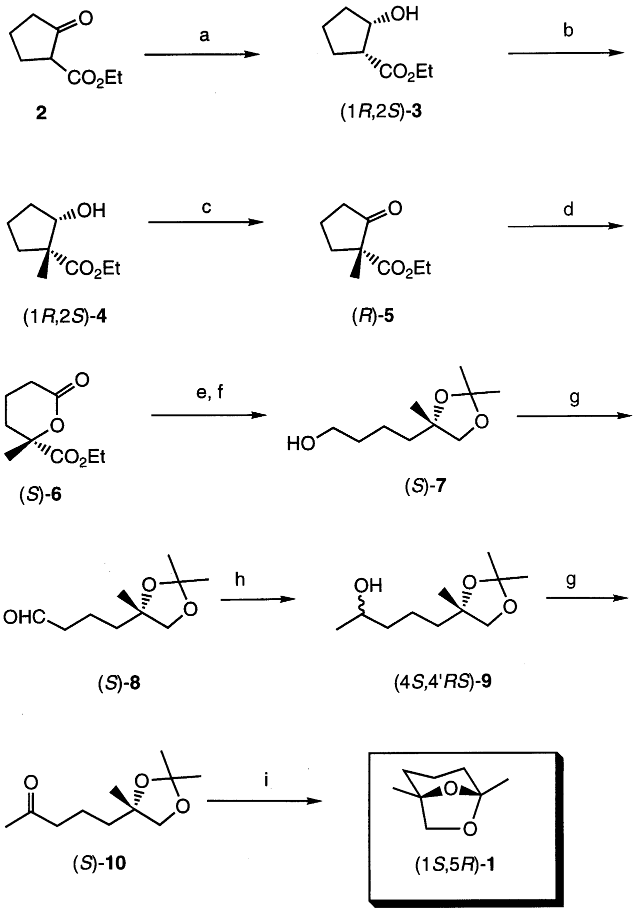
Scheme 2. Synthesis of (−)-frontalin (**1**)



Reagents: (a) Baker′s yeast, sucrose, H_2O (52%). − (b) 2.25 eq. LDA, 1.45 eq. MeI, THF (87%). − (c) Jones′ CrO_3, Me_2CO (87%). − (d) MCPBA, $NaHCO_3$, CH_2Cl_2 (59%). − (e) $LiAlH_4$, Et_2O. − (f) $Me_2C(OMe)_2$, Me_2CO, TsOH · H_2O (77%, 2 steps). − (g) PCC, NaOAc, molecular sieves 3 Å, CH_2Cl_2 (70% for **8**; 97% for **10**). − (h) MeMgBr, Et_2O (84%). − (i) TsOH · H_2O, Et_2O, H_2O (81%).

g, 74%) with 90.4% d.e. with b.p. 55−57°C/0.5 Torr and another fraction (8.4 g, 13%) with 78% d.e. and b.p. 57−65°C/0.5 Torr. We used **4** with about 89% d.e. for the next step. Jones oxidation of **4** furnished (*R*)-**5**[30]. The existing alternative synthesis of (*R*)-**5** is the methylation of the enamine derived from **2** and (*S*)-valine *tert*-butyl ester[34].

The Baeyer-Villiger oxidation of (*R*)-**5** with *m*-chloroperbenzoic acid (MCPBA) proceeded rather sluggishly as was observed by Solladié et al.[35] in the case of (±)-**5**, and gave the desired lactone (*S*)-**6** in 59% yield after 5 days′ stirring at 25°C in the presence of sodium hydrogen carbonate. Reduction of (*S*)-**6** with lithium tetrahydridoaluminate was followed by acetonide formation to give (*S*)-**7**, which was oxidized with pyridinium chlorochromate (PCC) to furnish (*S*)-**8**. Addition of methylmagnesium bromide to (*S*)-**8** afforded the alcohol **9**, which was oxidized with PCC to yield the methyl ketone (*S*)-**10**. Acid treatment of (*S*)-**10** gave the desired (1*S*,5*R*)-(−)-frontalin (**1**), whose enantiomeric purity was 89.1% e.e. as determined by GC analysis on a chiral stationary phase. We could prepare about 10 g of **1** in an overall yield of 7.8% based on **2** (10 steps). The biological study on the Jeffrey pine beetle using **1** and (+)-*exo*-brevicomin is in progress and the result will be published separately by Seybold.

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Experimental Section

General: Boiling points: uncorrected values. − IR: Perkin-Elmer 1640. − ^1H NMR: Jeol JNM-EX 90A (90 MHz) and Jeol JNM-EX 270L (270 MHz, TMS at $\delta_H = 0.00$ or $CHCl_3$ at $\delta_H = 7.26$ as an internal standard). − ^{13}C NMR: Jeol JNM-EX 270L (67.8 MHz, TMS as an internal standard). − MS: Hitachi M-80-B. − Optical rotation: Jasco DIP-1000. − Column chromatography: Merck Kieselgel 60 Art 1.07734. − TLC: 0.25 mm Merck silica-gel plates (60F-254).

Ethyl (1R,2S)-2-Hydroxycyclopentane-1-carboxylate (**3**): To a suspension of baker's yeast (dry yeast, Oriental yeast Co., 140 g) in a solution of sucrose (300 g) in tap water (2500 ml), **2** (27.2 g, 174 mmol) in ethyl alcohol (10 ml) was added dropwise with stirring. The mixture was stirred and aerated at 30°C for 12 h. Occasionally octyl alcohol (a few drops) was added to the suspension to suppress the foaming. The mixture was filtered through Celite and the filtration bed was washed with ethyl acetate. The combined filtrate and washings were washed with brine, dried with magnesium sulfate and concentrated in vacuo. The residue was distilled to give impure **3**. This was chromatographed on silica gel (300 g, AcOEt/hexane, 1:50), and the fractions containing **3** were further purified by distillation to give 14.4 g (52%) of **3**. − B.p. 76°C/4 Torr. − $[\alpha]_D^{22} = +14.5$ (c = 2.83, $CHCl_3$) {ref.[27] $[\alpha]_D = +14.7$ (c = 2.08, $CHCl_3$)}. − $n_D^{25} = 1.4534$. − IR (film): $\tilde{\nu}_{max} = 3480$ cm^{-1} (s, OH), 1730 (vs, CO−O). − ^1H NMR (90 MHz, $CDCl_3$): $\delta = 1.27$ (t, J = 7.1 Hz, 3 H, CH_2CH_3), 1.4−2.1 (m, 6 H, 3,4,5-H), 2.48−1.75 (m, 1 H, 1-H), 3.10 (d, J = 2.4 Hz, 1 H, −OH), 4.18 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 4.3−4.5 (m, 1 H, 2-H). − GLC (column: Chirasil-DEX CB®, 0.25 mm × 25 m, 1 min at 60°C, +3°C/min; carrier gas: He, pressure 110 kPa). t_R = 23.5 min [98.90%, (1*R*,2*S*)-**3**], t_R = 23.8 min. [1.10%, (1*S*,2*R*)-**3**], t_R = 27.5 min., 27.7 min. [0%, (1*R*,2*R*)-**3**, (1*S*,2*S*)-**3**]. The enantiomeric and diastereomeric purity of (+)-(1*R*,2*S*)-**3** were estimated to be 97.8% e.e. and 99% d.e.

Ethyl (1R,2S)-2-Hydroxy-1-methylcyclopentane-1-carboxylate (**4**): To a stirred and cooled solution of LDA prepared from diisopropylamine (120 ml, 853 mmol) in THF (300 ml) and *n*-butyllithium (3.04 M, 281 ml, 854 mmol) in hexane, a solution of **3** (60.0 g, 379 mmol) in THF (10 ml) was added in one portion at −50°C. The temperature was raised to −10°C and stirring was continued at this temperature. After 1 h, MeI (34.2 ml, 550 mmol) was added to the solution at −50°C and the mixture was warmed to room temp. The solution was stirred for 3 h, neutralized with satd. ammonium chloride solution and poured into water. It was then extracted with ethyl acetate, and the extract was washed with water, satd. ammonium chloride and brine, dried with magnesium sulfate, and concentrated in vacuo. The residue was distilled to give 48.0 g (74%) of **4** (90.4% d.e., b.p. 55−57°C/0.5 Torr) and 8.4 g (13%) of **4** (78% d.e., b.p. 57−65°C/0.5 Torr). The former **4** showed the following properties: $[\alpha]_D^{24} = +27.8$ (c = 1.27, $CHCl_3$) {ref.[30] $[\alpha]_D^{20} = +28.4$ (c = 1.61, $CHCl_3$)}. − $n_D^{24} = 1.4544$. − IR (film):

$\tilde{\nu}_{max}$ = 3480 cm^{-1}, 1730 (vs, CO−O), 1715 (vs, CO−O). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.18 (s, 3 H, 1-Me), 1.27 (t, J = 7.1 Hz, CH_2CH_3), 1.4−2.3 (m, 6 H, 3,4,5-H), 3.09 (d, J = 4.2 Hz, 1 H, OH), 3.9−4.0 (m, 1 H, 2-H), 4.18 (q, J = 7.1 Hz, 2 H, CH_2CH_3). − GLC (column: TC-Wax®, 0.35 mm × 15 m, 1 min at 80°C and 3°C/min; carrier gas: He, pressure 1.6 kPa) t_R = 4.56 min [(1*R*,2*S*)-**4**], t_R = 7.77 min [(1*S*,2*S*) -**4**].

Ethyl (R)-1-Methyl-2-oxocyclopentane-1-carboxylate (**5**): To a stirred and cooled solution of **4** (53.7 g, 312 mmol) in acetone (1300 ml), Jones' CrO_3 reagent (100 ml) was added dropwise at 0°C and the mixture was stirred for 1 h at room temp. The reaction was quenched by the addition of 2-propanol and the mixture was concentrated in vacuo. The residue was diluted with water and extracted with diethyl ether. The ethereal extracts were washed with water, satd sodium hydrogen carbonate and brine, dried with magnesium sulfate, and concentrated in vacuo. The residue was distilled to give 46.4 g of **5** (87%). − B.p. 76−78°C/3.5 Torr. − $[\alpha]_D^{24}$ = −15.9 (c = 1.72, $CHCl_3$) {ref.[30] $[\alpha]_D^{20}$ = −13.3 (c = 1.09, $CHCl_3$)}. − n_D^{24} = 1.4452. − IR (film): $\tilde{\nu}_{max}$ = 1750 cm^{-1} (vs, CO), 1730 (vs, CO). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.23 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 1.29 (s, 3 H, 1-Me), 1.6−2.6 (m, 6 H, 3,4,5-H), 4.14 (q, J = 7.2 Hz, 2 H, CH_2CH_3).

(S)-5-Ethoxycarbonyl-5-hexanolide (**6**): A solution of **5** (32.2 g, 189 mmol) in CH_2Cl_2 (50 ml) was added dropwise to a stirred mixture of 80% MCPBA (62.1 g, 288 mmol) and sodium hydrogen carbonate (20.0 g, 238 mmol) in CH_2Cl_2 (1000 ml) at 0°C and the mixture was stirred at room temp. After 2 d, 80% MCPBA (10 g, 57.9 mmol) was added again and the mixture was further stirred for 3 d. It was then filtered through Celite and the filtration bed was washed with diethyl ether. The combined filtrate and washings were washed with 0.1 N aqueous sodium thiosulfate solution, 0.1 N aqueous sodium hydroxide solution, satd. sodium hydrogen carbonate, water and brine, dried with magnesium sulfate, and concentrated in vacuo. The residue was distilled to give 20.6 g of **5** (59%). − B.p. 120°C/4.5 Torr. − $[\alpha]_D^{23}$ = +9.10 (c = 1.59, $CHCl_3$). − n_D^{23} = 1.4554. − IR (film): $\tilde{\nu}_{max}$ = 1750 cm^{-1} (vs, CO−O). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.30 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 1.62 (s, 3 H, 5-Me), 1.5−2.6 (m, 6 H, 2,3,4-H), 4.26 (q, J = 7.1 Hz, 2 H, CH_2CH_3). − $C_9H_{14}O_4$ (186.2): calcd. C 58.05, H 7.58; found C 57.31, H 7.54. − HR MS; m/z: found 186.0884 [M$^+$]; calcd. 186.0892.

(S)-4-(4'-Hydroxybutyl)-2,2,4-trimethyl-1,3-dioxolane (**7**): A solution of **6** (27.5 g, 148 mmol) in THF (100 ml) was added dropwise to a stirred and cooled suspension of lithium tetrahydridoaluminate (9.25 g, 77.7 mmol) in dry THF (900 ml) at 0°C and the mixture was stirred at room temp. for 10 h. Then the mixture was stirred under reflux for 1 h, and quenched with water (10 ml), 0.1 N aqueous sodium hydroxide solution (10 ml) and water (30 ml) at 0°C. The suspension was filtered through Celite and the filtration bed was washed with diethyl ether. The combined filtrate and washings were concentrated in vacuo to give a crude triol (20.2 g), which was employed in the next step without further purification. *p*-Toluenesulfonic acid monohydrate (0.1 g) was added to a solution of the crude triol (20.1 g, 136 mmol) and 2,2-dimethoxypropane (17.4 ml, 142 mmol) in acetone (300 ml) and the mixture was stirred at room temp. for 1 h. The solvent was then removed by evaporation in vacuo. The residue was diluted with satd. sodium hydrogen carbonate and extracted with diethyl ether. The ethereal extracts were washed with satd. sodium hydrogen carbonate, water and brine, dried with magnesium sulfate and concentrated in vacuo. The residue was distilled to give 21.5 g of **7** (77%, 2 steps). − B.p. 104−106°C/2 Torr. − $[\alpha]_D^{24}$ = −2.57 (c = 1.11, $CHCl_3$). − n_D^{24} = 1.4444. − IR (film): $\tilde{\nu}_{max}$ = 3420 cm^{-1} (s, OH), 1060 (vs, C−O−C). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.29 (s, 3 H, Me), 1.40 (s, 6 H, Me_2), 1.4−1.7 (m, 6 H, 1',2',3'-H), 3.68 (d, J = 8.6 Hz, 1 H, 5-H), 3.80 (d, J = 8.6 Hz, 1 H, 5-H), 3.5−3.8 (m, 2 H, 4'-H). − $C_{10}H_{20}O_3$ (188.3): calcd. C 63.80, H 10.71; found C 63.26, H 10.22.

(S)-2,2,4-Trimethyl-4-(4'-oxobutyl)-1,3-dioxolane (**8**): A solution of **7** (10.2 g, 54.8 mmol) in dichloromethane (20 ml) was added dropwise to the stirred and cooled suspension of sodium acetate (1.56 g), powdered molecular sieves 3 Å (30 g) and PCC (23.4 g, 109 mmol) in dichloromethane (300 ml) at 0°C, and the mixture was stirred at room temp. for 6 h. Then this suspension was filtered through silica gel and the filtration bed was washed with diethyl ether. The combined filtrate and washings were washed with satd. aqueous sodium thiosulfate solution, water, satd. sodium hydrogen carbonate and brine, dried with magnesium sulfate and concentrated in vacuo. The residue was distilled to give 7.1 g of **8** (70%). − B.p. 70°C/3Torr. − $[\alpha]_D^{24}$ = −1.94 (c = 1.25, $CHCl_3$). − n_D^{24} = 1.4372. − IR (film): $\tilde{\nu}_{max}$ = 1725 cm^{-1} (vs, CO), 1060 (vs, C−O−C). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.28 (s, 3 H, Me), 1.38 (s, 6 H, Me_2), 1.4−1.9 (m, 4 H, 1',2',-H), 2.37−2.58 (m, 2 H, 3'-H), 3.69 (d, J = 8.4 Hz, 1 H, 5-H), 3.81 (d, J = 8.4 Hz, 1 H, 5-H), 9.78 (t, J = 1.6 Hz, 1 H, CHO). − $C_{10}H_{18}O_3$ (186.3): calcd. C 64.49, H 9.74; found C 64.49, H 10.12.

(4S,4'RS)-4-(4'-Hydroxypentyl)-2,2,4-trimethyl-1,3-dioxolane (**9**): To a stirred and cooled solution of **8** (12.5 g, 67.1 mmol) in THF (400 ml), methylmagnesium bromide (0.92 M, 95 ml, 87.4 mmol) was added dropwise at −20°C, and the mixture was stirred at room temp. for 30 min. Then satd. ammonium chloride solution was added and the reaction mixture was poured into water and extracted with diethyl ether. The ethereal extracts were washed with water and brine, dried with magnesium sulfate and concentrated in vacuo. The residue was distilled to give 11.3 g of **9** (84%). − B.p. 98−102°C/5 Torr. − $[\alpha]_D^{23}$ = −2.13 (c = 1.50, $CHCl_3$). − n_D^{24} = 1.4423. − IR (film): $\tilde{\nu}_{max}$ = 3445 cm^{-1} (s, OH), 1060 (vs, C−O−C). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.19 (d, J = 6.2 Hz, 3 H, 5'-H), 1.28 (s, 3 H, Me), 1.39 (s, 6 H, Me_2), 1.3−1.7 (m, 6 H, 1',2',3'-H), 3.69 (d, J = 8.4 Hz, 1 H, 5-H), 3.80 (d, J = 8.4 Hz, 1 H, 5-H), 3.5−4.0 (m, H, 4'-H). − $C_{11}H_{22}O_3$ (202.3): calcd. C 65.31, H 10.96; found C 65.24, H 11.19.

(S)-2,2,4-Trimethyl-4-(4'-oxopentyl)-1,3-dioxolane (**10**): To a stirred and cooled suspension of sodium acetate (2.06 g), powdered molecular sieves 3 Å (30 g) and PCC (17.0 g, 78.9 mmol) in dichloromethane (300 ml), a solution of **9** (8.10 g, 39.6 mmol) in dichloromethane (20 ml) was added at 0°C and the mixture was stirred at room temp. After 9 h, this suspension was filtered through silica gel and the filtration bed was washed with diethyl ether. The combined filtrate and washings were washed with satd. aqueous sodium thiosulfate solution, water, satd. sodium hydrogen carbonate and brine, dried with magnesium sulfate and concentrated in vacuo. The residue was distilled in the presence of magnesium carbonate to give 7.75 g (97%) of **10**. − B.p. 85−87°C/4 Torr. − $[\alpha]_D^{23}$ = −0.54 (c = 1.08, $CHCl_3$) {ref.[28] $[\alpha]_D^{23}$ = −0.90 (c = 9.54, $CHCl_3$)}. − n_D^{23} = 1.4364. − IR (film): $\tilde{\nu}_{max}$ = 1715 cm^{-1} (vs, C=O). 1060 (s, C−O−C). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.27 (s, 3 H, Me), 1.37 (s, 6 H, Me_2), 1.5−1.9 (m, 4 H, 1',2'-H), 2.13 (s, 3 H, 5'-H), 2.38−2.56 (m, 2 H, 3'-H), 3.68 (d, J = 8.4 Hz, 1 H, 5-H), 3.80 (d, J = 8.4 Hz, 1 H, 5-H).

(−)-*Frontalin* [(1*S*,5*R*)-1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane (**1**)]: A stirred mixture of **10** (7.72 g, 38.5 mmol), *p*-toluenesulfonic acid monohydrate (2 g) in water (6 ml) and diethyl ether (400 ml) was refluxed for 3 h. It was subsequently washed with satd. sodium hydrogen carbonate and brine, then dried with magnesium sulfate. The solvent was removed at atmospheric pressure, and the residue was distilled to give 4.45 g (81%) of **1**. − B.p. 86−87°C/99 Torr. − $[\alpha]_D^{24} = -50.3$ (c = 1.63, Et_2O) {ref.[28] $[\alpha]_D^{23} = -51.7$ (c = 2.2, Et_2O)}. − $n_D^{24} = 1.4368$. − IR (film): $\tilde{\nu}_{max} = 2975$ cm^{-1} (m), 2935 (s), 2875 (m), 1455 (w), 1385 (m), 1380 (m), 1345 (w), 1285 (w), 1260 (m), 1240 (m), 1205 (m), 1175 (m), 1120 (s), 1065 (m), 1030 (vs, C−O−C), 930 (m), 895 (m), 870 (m), 820 (m), 850 (s), 820 (m), 610 (w) − ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.33 (s, 3 H, 1-Me), 1.44 (s, 3 H, 5-Me), 1.49−2.00 (m, 6 H, 2,3,4-H), 3.46 (dd, J = 6.8, 1.6 Hz, 1 H, 7-H,), 3.84 (d, J = 6.8 Hz, 1 H, 7-H). − ^{13}C NMR (67.5 MHz): δ = 18.0, 23.1, 24.7, 33.9, 34.6, 74.2, 80.1, 108.1. − GLC (column: Chirasil-DEX CB®, 0.25 mm × 25 m, 90°C; carrier gas: He, pressure 110 kPa): t_R = 9.17 min [94.55%, (1*S*,5*R*)-**1**], t_R = 9.28 min [5.45%, (1*R*,5*S*)-**1**]. The enantiomeric purity of (−)-(1*S*,5*R*)-**1** was estimated to be 89.1% e.e.

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