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PHEROMONE SYNTHESIS—63

SYNTHESIS OF BOTH THE ENANTIOMERS OF 2,3-DIHYDRO-2-ISOPROPYL-2,5-DIMETHYLFURAN, A SEX SPECIFIC COMPOUND IN FEMALES OF THE BEETLE *HYLECOETUS DERMESTOIDES* L†

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Abstract—Both the enantiomers of 2,3-dihydro-2-isopropyl-2,5-dimethylfuran were synthesized employing the Sharpless asymmetric epoxidation reaction. The (*R*)-(−)-enantiomer of this cyclic enol ether was also synthesized starting from (*R*)-(−)-linalool.

A cyclic enol ether, 2,5 - dimethyl - 2 - isopropyl - 2,3-dihydrofuran **1**, was isolated by Francke as a sex specific compound in females of the beetle *Hylecoetus dermestoides* L.[1] This polyphagous insect is frequently found on weakened trees, logs and stumps both of hardwood and softwood in middle Europe. The proposed structure **1** was confirmed by a synthesis of its racemate.[2] A synthesis of its (*S*)-enantiomer from D-glucose was also reported by Redlich *et al.*[2,3]

As a part of our continuing study on the stereochemistry–pheromone activity relationship,[4] we undertook the synthesis of both the enantiomers of **1** starting from a single (*S*)-epoxide **2** (Fig. 1). To confirm the (*R*)-configuration of our synthetic (−)-**1**, an alternative synthesis of (*R*)-(−)-**1** was also achieved starting from (*R*)-(−)-linalool **3**.

The synthesis of both the enantiomers of **1** from **2** is shown in Fig. 2. The Sharpless asymmetric epoxidation[5] of an allylic alcohol **4**[6] with diethyl L-(+)-tartrate as the chiral auxiliary yielded (*S*)-(−)-**2** in 56% yield. Besides **2**, a varying amount of an isopropyl ether **i** was obtained as a by-product. This could be removed by the careful fractional distillation of the product. In our large-scale preparation of **2**, **4** (0.40 mole) was epoxidized with t-BuOOH (0.88 mole) in the presence of 0.48 mole of diethyl L-(+)-tartrate and 0.26 mole (0.65 eq) of $Ti(OPr^i)_4$. The presence of an increased amount (1.0 eq) of $Ti(OPr^i)_4$ could greatly improve neither chemical nor optical yields of **2** (28.3% yield with ~88% optical purity). The increased amount of $Ti(OPr^i)_4$ caused an undesired increase in the amount of the by-product **i**. A portion of **2** was acylated with an acyl chloride derived from (*S*) - (−) - α - methoxy - α - trifluoromethylphenylacetic acid (MTPA).[7] HPLC analysis of the resulting ester revealed the optical purity of (*S*)-**2** to be 86%. The epoxide **2** was reduced with LAH to give a diol **5a** in 87% yield. The optical purity of this diol **5a** was determined to be 86% also by analyzing the corresponsing mono MTPA ester of **5a** by HPLC. Tosylation of **5a** yielded a monotosylate **5b**. This was treated with $(CH_2{=}CHCH_2)_2CuLi$ prepared from $CH_2{=}CHCH_2Li$[8] and CuI to give an olefinic alcohol (*R*)-**6** in 66% yield from **5a**. For the preparation of (*S*)-**6** the epoxide **2** was treated with $(CH_2{=}CHCH_2)_2CuLi$ to give a diol **7a** in 88% yield. The corresponding monotosylate **7b** was reduced with LAH to give (*S*)-**6**.

Conversion of **6** to the desired enol ether **1** was executed as follows. Oxidation of **6** by the Pd-catalyzed Wacker process (O_2 in the presence of $PdCl_2$–CuCl in DMF–H_2O)[9] afforded a ketone **8** after chromatographic purification over SiO_2. ^{13}C-NMR measurement of (*S*)-**8** indicated that, in a $CDCl_3$ soln, **8** is in equilibrium with **ii** and **iii** in *ca* 1:1:1 ratio (see Experimental). Distillation of **8** in the presence of anhyd $CaSO_4$ effected cyclization and dehydration to give **1** in 21 ~ 26% yield from **6**. Our synthetic **1** showed an entirely identical MS to that reported for the natural product.[1,2] The optical rotations observed for our synthetic enol ethers were: $[\alpha]_D^{22} - 8.6°$ (c = 0.76, pentane) for (*R*)-**1**, and $[\alpha]_D^{22} + 9.3°$ (c = 0.85, pentane) for (*S*)-**1**. Previously, however, Redlich *et al.* reported the specific rotation of their synthetic (*S*)-**1** to be $[\alpha]_D^{23} - 1.1°$ (c = 0.83, pentane).[2,3] This opposite sign of the rotation embarassed us, because it might mean that our assignment of the absolute configuration basing on the steric course of the Sharpless epoxidation was incorrect.

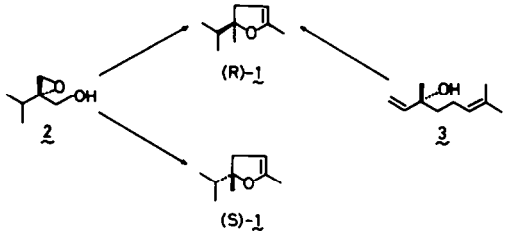

Fig. 1. Synthetic plan.

†Part 62: S. Kuwahara and K. Mori, *Agric. Biol. Chem.* **47**, 2599 (1983).

In order to ascertain the absolute configuration of our synthetic enantiomers (+)- and (−)-**1**, two independent experiments were carried out (Fig. 3). The first attempt was to correlate the absolute configuration of **5a** with that of a hydroxy acid **11**.[10] The known hydroxy acid **11** was prepared from methyl isopropyl ketone **9** via a cyanohydrin **10**. The racemic acid (±)-**11** was resolved with optically pure α-phenylethylamine in *i*-PrOH to give (+)-**11**, $[\alpha]_D^{20}$ + 7.1° ($CHCl_3$) [lit[11] $[\alpha]_D^{20}$ + 4.57° ($CHCl_3$)] and (−)-**11**, $[\alpha]_D^{20}$ − 7.1° ($CHCl_3$). The absolute configuration of the resolved acid was deduced from its CD spectrum. α-Hydroxy acids with the (*S*)-configuration were known to exhibit a positive Cotton effect observed near 200 nm, while acids with the (*R*)-configuration show a negative effect.[12] Our (+)-acid **11** showed a positive Cotton effect at 209 nm, while (−)-**11** exhibited a negative effect. The (*S*)-configuration was therefore assigned to (+)-**11** and the (*R*)-configuration to its antipode. Reduction of (*S*)-(+)-**11** with LAH yielded the (−)-diol **5a**, $[\alpha]_D^{21}$ − 13.4° ($CHCl_3$), which was identical in every respect with (−)-**5a**, $[\alpha]_D^{22}$ − 12.1° ($CHCl_3$), prepared via Sharpless epoxidation. Reduction of (*R*)-(−)-**11** with LAH gave the (+)-diol **5a**, $[\alpha]_D^{21}$ + 13.9° ($CHCl_3$). The (*S*)-configuration of (+)-**1** was thus supported by the CD of (+)-**11**. It should be added that this experiment constitutes a formal synthesis of both (*R*)- and (*S*)-**1** via optical resolution.

The second and more direct confirmation of the (*R*)-configuration of (−)-**1** was its alternative synthesis from (*R*) - (−) - linalool **3**. The Sharpless epoxidation[13] of **3** with t-BuOOH–VO(acac)$_2$ gave **12** in 52% yield. This was reduced with LAH to give a diol **13a**. Tosylation of **13a** yielded a monotosylate **13b**. Treatment of **13b** with $Me_2Cu(CN)Li_2$ resulted in the clean displacement of the TsO group with a Me group to give **14** in 80% yield from **13a**.[14] Oxidation of **14** with $RuCl_3$–$NaIO_4$ under the Sharpless condition[15] gave a lactone **15** in 80% yield. This was hydrolyzed with LiOH and the resulting Li salt of the corresponding hydroxy acid was thoroughly dried. It was then treated with MeLi to give (*R*)-**8**. Finally, distillation of **8** over anhyd $CaSO_4$ yielded pure (*R*)-**1**, $[\alpha]_D^{24}$ − 8.1° (pentane). This alternative synthesis again supported our conclusion that (−)-**1** is the (*R*)-enantiomer. It also indicated that the steric course of the Sharpless epoxidation of **4** was not abnormal but normal. The contrary claim by Redlich *et al.*[2,3] might have been due to the following three facts. (i) The enol ether **1** is sensitive to moisture and gives back **8**. (ii) The hydroxy ketone **8**, upon GLC analysis, cyclizes and loses H_2O to give the enol ether **1**. Indeed, upon GLC–MS analysis, **8** showed the MS identical to that of **1**. (iii) The sign of the rotation of (*S*)-**8** was not positive but negative: $[\alpha]_D^{23}$ − 5.52° (pentane), while (*S*)-**1** was dextrorotatory. Possibly Redlich's (*S*)-**1** employed for the $[\alpha]_D$ measurement was mixture of (*S*)-**8** and (*S*)-**1**.

In conclusion, both the enantiomers of **1** were

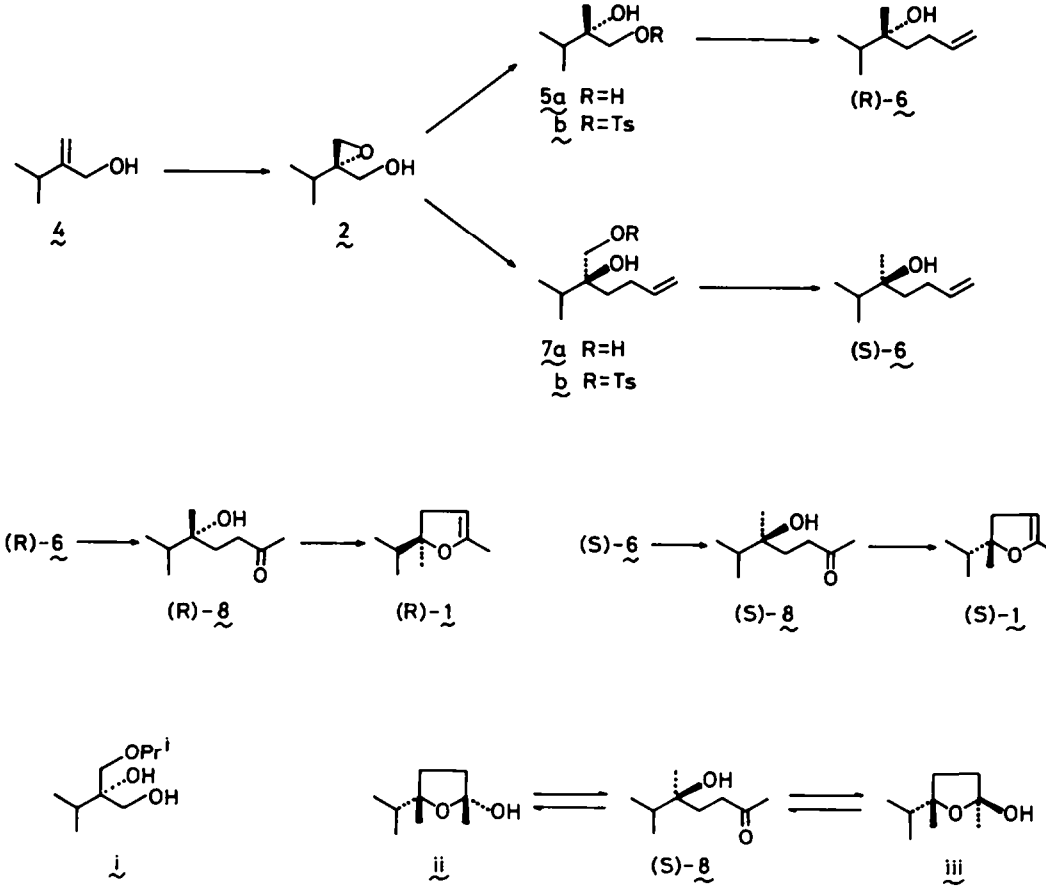

Fig. 2. A synthesis by means fo the Sharpless epoxidation.

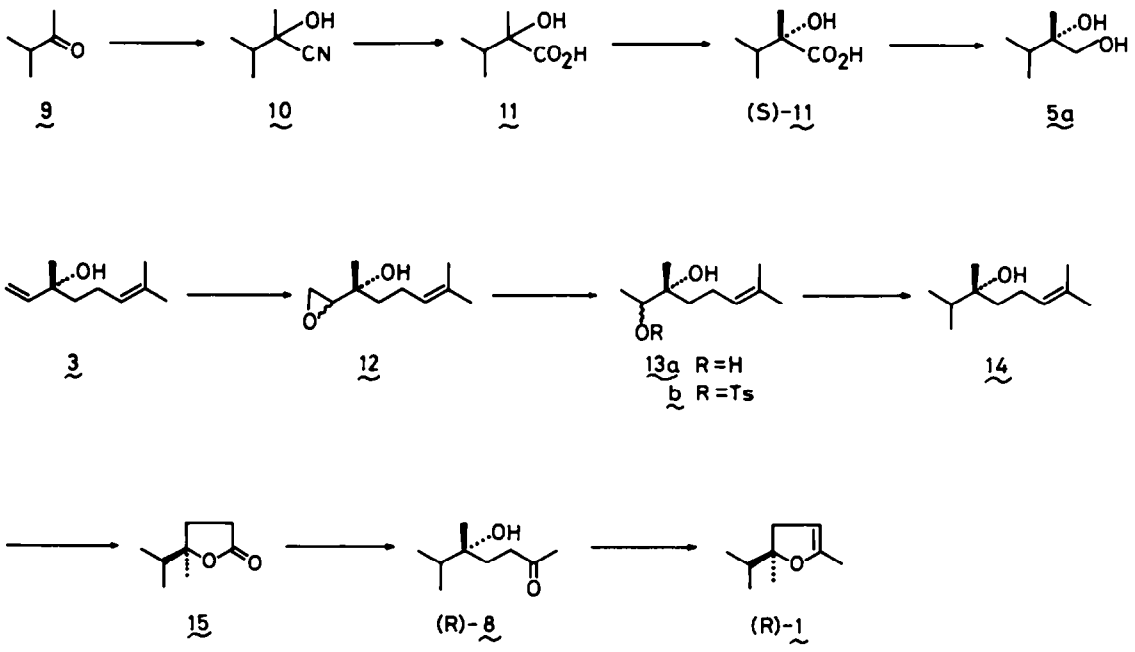

Fig. 3. Syntheses by means of the optical resolution of an intermediate or the derivation from (*R*)-(−)-linalool.

synthesized in sufficient quantities to test their biological properties. The bioassay is now under way in Prof. J. P. Vité's laboratory (University of Freiburg i-Br.) through the courtesy of Dr. W. Francke.

EXPERIMENTAL

All m.ps and b.ps were uncorrected. IR spectra were measured as Nujol mulls (solid) or as films (liquid) on a Jasco A-102 spectrometer. NMR spectra were recorded at 60 MHz as CCl_4 soln with TMS as an internal standard on a Hitachi R-24A spectrometer unless otherwise stated. Optical rotations were measured on a Jasco DIP-181 polarimeter. GLC analyses were performed on a Yanaco G-80 gas chromatograph. GLC-MS was measured on a JMS-DX 300 apparatus.

(S)-(−)-2,3-*Epoxy*-2-*isopropyl*-1-*propanol* **2**

$Ti(OPr^i)_4$ (76.4 ml) and diethyl L-(+)-tartrate (98.9 g) were added to dry CH_2Cl_2 (1600 ml) with stirring at −23° under Ar and stirred for 5 min. To the mixture, **4** (40 g) and a CH_2Cl_2 soln of anhyd t-BuOOH (4.09 N, 215 ml) were added. The mixture was stored at −30° for 68 hr. Me_2S (116 ml) was then added to the stirred and cooled mixture at −23°. After stirring for 1 h at −23°, the cold mixture was added slowly to a vigorously stirred sat NaF aq (2000 ml) at room temp. The stirring was continued for 1 h and then the aq phase was saturated with NaCl. This was filtered to remove the insoluble material. The organic layer of the filtrate was separated and the aq layer was extracted with CH_2Cl_2. The combined organic soln was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Merck Kieselgel 60, 1.3 kg). Elution with n-hexane–ether (10:1, 3:2) gave **2**. This was fractionally distilled through a Vigreux column to give 26.0 g (56.0%) of pure **2**, b.p. 68 ~ 70°/10 mm, n_D^{22} 1.4337; $[\alpha]_D^{22}$ − 37.3° (c = 0.92, $CHCl_3$); ν_{max} ~ 3430 (s), 1045 (s) cm^{-1}; δ 0.89 (3H, d, J = 7 Hz), 0.96 (3H, d, J = 7 Hz), 1.86 (1H, sept, J = 7 Hz), 2.53 (1H, d, J = 5 Hz), 2.73 (1H, d, J = 5 Hz), 3.41 (1H, br), 3.59 (2H, br). (Found: C, 61.72; H, 10.44. Calc for $C_6H_{12}O_2$: C, 62.04; H, 10.41%.) As a by-product, **i** (**1**:**2** = 7:93) was obtained. This seemed to be produced during the NaF treatment. If the mixture was treated with NaF overnight at room temp, more **i** was obtained (**i**:**2** = 1:1). This could be removed by careful fractional distillation and showed the following properties: b.p. 91 ~ 92°/5 mm, $[\alpha]_D^{22}$ + 7.59° (c = 1.08, $CHCl_3$); ν_{max} ~ 3440 (s), 1125 (s), 1080 (s), 1060 (sh), 1020 (s) cm^{-1}; δ 0.90 (6H, d, J = 7 Hz), 1.15 (6H, d, J = 6 Hz), 1.5 ~ 2.2 (1H, m), 2.9 ~ 3.9 (7H, m).

Determination of the optical purity of (S)-(−)-**2**

The MTPA esters of (±)-**2** and (*S*)-(−)-**2** were prepared in the usual manner using (*S*)-(−)-MTPA, and analyzed by HPLC (Column, Partisil 5, 25 cm × 4.6 mm; Eluent, *n*-hexane-THF = 40:1; Flow rate, 1 ml/min): HPLC of (±)-**2** MTPA ester: R_t 50.4 min and 56.8 min (1:1). HPLC of (*S*)-(−)-**2** MTPA ester: R_t 49.2 min (93%) and 55.2 min (7%). Optical purity of (*S*)-(−)-**2** = 86%.

(S)-(−)-2,3-*Dimethyl*-1,2-*butanediol* **5a**

A soln of **2** (2.31 g) in dry ether (40 ml) was added dropwise to a suspension of LAH (1.14 g) in dry ether (100 ml) with stirring and ice-cooling. The mixture was stirred overnight at room temp. Then H_2O (1.5 ml), 2 N NaOH (3 ml) and H_2O (1.5 ml) were added dropwise to the stirred and ice-cooled mixture. After stirring for 2.5 h, the mixture was filtered and the filter-cake was thoroughly washed with THF. The combined filtrate and washings were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was distilled to give 2.05 g (87.3%) of **5a**, b.p. 69 ~ 71°/1.0 mm, n_D^{23} 1.4426; $[\alpha]_D^{22}$ − 12.1° (c = 1.01, $CHCl_3$); ν_{max} ~ 3400 (br, s), 1095 (m), 1055 (s), 1025 (s) cm^{-1}; δ 0.83 (3H, d, J = 7 Hz), 0.92 (3H, d, J = 7 Hz), 0.97 (3H, s), 1.45 ~ 2.10 (1H, m), 3.38 (2H, br), 3.57 (1H, br), 4.24 (1H, br). (Found: C, 60.97; H, 11.97. Calc for $C_6H_{14}O_2$: C, 60.98; H, 11.94%.)

Determination of the optical purity of (S)-(−)-**5a**

The MTPA ester of (*S*)-(−)-**5a** was prepared in the usual manner using (*S*)-(−)-MTPA. HPLC (Column, Partisil 5, 25 cm × 4.6 mm; Eluent, n-hexane–THF = 40:1;

Flow rate, 3 ml/min): R_t 71.6 min (~93%), 76.4 min (~7%). Optical purity of (*S*) - (−) - **5a** = 86%.

(S)-2,3-*Dimethyl*-1-*tosyloxy*-2-*butanol* **5b**

p-TsCl (7.62 g) was added to a stirred and ice-cooled soln of **5a** (3.60 g) in dry C_5H_5N (20 ml). The stirring was continued overnight at 5°. The mixture was diluted with ether (40 ml) and N HCl (40 ml). The organic layer was separated and the aq layer was extracted. The combined organic soln was washed with $CuSO_4$ soln, water and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 8.30 g of crude **5b**, ν_{max} 3550 (m), 1600 (m), 1360 (s), 1190 (s), 1175 (s), 980 (s) cm^{-1}. This was employed in the next step without further purification.

(R)-(−)-2,3-*Dimethyl*-6-*hepten*-3-*ol* **6**

A soln of CH_2=$CHCH_2Li$ in dry ether was prepared by the addition of n-BuLi (1.59 M in hexane, 271 ml) to a soln of Ph_3SnCH_2CH=CH_2 (169 g) in dry ether (1400 ml).[8] This (0.26 M, 769 ml) was added to a stirred and cooled suspension of CuI (19.0 g) in dry ether (200 ml) at −60 ~ −70° under Ar and the mixture was stirred for 1.5 h at this temp. A soln of **5b** (8.30 g) in dry ether (20 ml) was added dropwise to the mixture at −65 ~ −70°. The reaction temp was then gradually raised to room temp. The mixture was stirred overnight and poured into ice and sat NH_4Cl soln. This was stirred for 30 min and filtered to remove the insoluble material. The filtrate was extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and fractionated under atmospheric pressure with a Vigreux column. The residue was chromatographed over SiO_2 (Merck Kieselgel 60, 800 g). Elution with n-hexane–ether (20:1 ~ 5:1) gave (*R*)-**6**, which was distilled to give 2.86 g (66.1% from **5a**) of pure (*R*)-**6**, b.p. 94 ~ 96°/49 mm, n_D^{23} 1.4430; $[\alpha]_D^{23}$ − 5.1° (c = 0.95, $CHCl_3$); ν_{max} ~ 3430 (br s), 3080 (m), 2975 (s), 2950 (s), 2880 (m), 1640 (m), 1155 (m), 1130 (sh), ~ 1090 (m), 995 (m), 910 (s) cm^{-1}: δ 0.86 (3H, d, J = 7 Hz), 0.88 (3H, d, J = 7 Hz), 1.02 (3H, s), 1.20 ~ 2.40 (6H, m), 4.70 ~ 5.15 (2H, m), 5.44 ~ 6.25 (1H, m). (Found: C, 75.76; H, 12.73. Calc for $C_9H_{18}O$: C, 75.99; H, 12.76%.)

(S)-(−)-2-*Isopropyl*-5-*hexene*-1,2-*diol* **7a**

A soln of CH_2=$CHCH_2Li$ in dry ether was prepared by the addition of n-BuLi (1.34 M in hexane, 220 ml, and 1.67 M in hexane, 77 ml) to a soln of Ph_3SnCH_2CH=CH_2 (166 g) in dry ether (1000 ml).[8] This (0.31 M, 684 ml) was added to a stirred and cooled suspension of CuI (20.1 g) in dry ether (200 ml) at −60 ~ −70° under Ar and the mixture was stirred for 1.5 h at this temp. A soln of **2** (4.1 g) in dry ether (20 ml) was added dropwise to the mixture at −65 ~ −70°. The reaction temp was then gradually raised to room temp. The reaction mixture was further stirred overnight and then poured into a mixture of sat NH_4Cl soln and ice. This was stirred for 30 min and filtered to remove the insoluble material. The filtrate was extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Merck Kieselgel 60, 800 g). Elution with n-hexane–ether (10:1 ~ 1:1) gave **7a**, which was distilled to give 4.92 g (88.2%) of pure **7a** b.p. 81 ~ 84°/0.45 mm, n_D^{22} 1.4635; $[\alpha]_D^{22}$ − 2.1° (c = 1.02, $CHCl_3$); ν_{max} ~ 3420 (br s), 3080 (w), 2960 (s), 2890 (m), 1642 (m), 1055 (s), 910 (s) cm^{-1}; δ 0.96 (6H, d, J = 7 Hz), 1.13 ~ 2.40 (5H, m), 2.98 (1H, br s), 3.46 (2H, br), 3.67 (1H, br), 4.74 ~ 5.30 (2H, m), 5.40 ~ 6.23 (1H, m). (Found: C, 67.96; H, 11.48. Calc for $C_9H_{18}O_2$: C, 68.31; H, 11.47%.)

(S)-2-*Isopropyl*-1-*tosyloxy*-5-*hexen*-2-*ol* **7b**

p-TsCl (6.96 g) was added to a stirred and ice-cooled soln of **7a** (4.40 g) in dry C_5H_5N (20 ml). The stirring was continued overnight at 5°. The mixture was diluted with ether (40 ml) and poured into N HCl (40 ml). The organic layer was separated and the aq layer was extracted with ether. The combined organic soln was washed with $CuSO_4$ soln, water and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 10.4 g of crude **7b**, ν_{max} 3550 (m), 1645 (m), 1600 (m), 1365 (m), 1190 (s), 1175 (s), 975 (s), 835 (s), 815 (s) cm^{-1}. This was employed in the next step without further purification.

(S)-(+)-2-*Isopropyl*-5-*hexen*-2-*ol* **6**

A soln of **7b** (10.4 g) in dry ether (80 ml) was added dropwise to a suspension of LAH (2.12 g) in dry ether (150 ml) with stirring and ice-cooling. The mixture was stirred overnight at room temp. Then H_2O (2 ml), 2 N NaOH (4 ml) and H_2O (2 ml) were added dropwise in this order to the stirred and ice-cooled mixture. After stirring for 2.5 h, the mixture was filtered and the filter-cake was washed with ether repeatedly. The combined filtrate and washings were dried (Na_2SO_4) and fractionated under atmospheric pressure with a Vigreux column. The residue was fractionally distilled with a Vigreux column to give 3.74 g (94.7% from **7a**) of pure (*S*)-**6**, b.p. 96 ~ 97°/50 mm, n_D^{22} 1.4439; $[\alpha]_D^{22}$ + 5.4° (c = 1.00, $CHCl_3$). The IR and NMR spectra were identical to those described for (*R*) - (−) - **6**.

(R)-(+)-5,6-*Dimethyl*-5-*hydroxy*-2-*heptanone* **8**

CuCl (1.01 g) and $PdCl_2$ (289 mg) were suspended in DMF (5 ml) and H_2O (0.5 ml). The mixture was stirred at room temp under O_2 until O_2 absorption ceased. Subsequently a soln of (*R*)-**6** (1.45 g) in DMF (2 ml) and H_2O (0.2 ml) was added to the mixture under ice-cooling. After stirring overnight at room temp, the mixture was diluted with ether (20 ml) and filtered to remove the insoluble material. The filtrate was washed with brine, dried ($MgSO_4$) and fractionated under atmospheric pressure with a Vigreux column to remove ether. The residue was chromatographed over SiO_2 (Merck Kieselgel 60, 40 g). Elution with n-pentane–ether (10:1 ~ 8:1) gave (*R*)-**8**, which was immediately distilled in the presence of $CaSO_4$ (1.0 g) to give 301 mg (21.0% from **6**) of (*R*)-**1**. In the presence of moisture, (*R*)-**1** gave back (*R*)-**8**, $[\alpha]_D^{22}$ + 4.16° (c = 0.77, pentane), ν_{max} ~ 3430 (br s), 2980 (s), 2880 (s), 1705 (m), 1370 (s), 1110 (s), 915 (s) cm^{-1}. The finger-print region of the IR spectrum of (*R*)-**8** was quite different from that of (*R*)-**1**. ^{1}H-NMR spectrum of (*R*)-**8** lacked signals due to C=C**H** and C=CC**H**$_3$ and exhibited a signal due to C**H**$_3$C = O at δ 2.12. ^{13}C-NMR spectrum of (*R*)-**8** was measured on a Jeol FX-100 at 25 MHz as a $CDCl_3$ soln. Although the spectrum of (*R*)-**8** was rather complicated due to the formation of an equilibrium mixture of **ii**, **iii** and **8**, the following signals could be observed: two signals due to **8** [δ 74.06 (C–OH, relative intensity = 100), 209.9 (C=O, rel int = 70.7)], and **ii** or **iii** [δ 104.8 (93.5), 105.4 (95.5) due to C(OH)O and δ 87.70 (82.3), 87.99 (90.2) due to C–O]. This ^{13}C-NMR data indicated *ca* 1:1:1 ratio of **ii**, **8** and **iii**. GLC (column, 3% SE-30, 1.5 m × 2 mm at 60 ~ 200°, + 10°/min; carrier gas, N_2, 0.8 kg/cm^2): R_t 2.3 min (*cf* R, of (*R*)-**6** under the same conditions: 4.2 min); GLC–MS (measured on Hitachi RMU-6E at 70 eV; column, SE-30, 1 m at 70°; carrier gas, He, 0.8 kg/cm^2): MS was identical with that of (*R*)-**1**.

(R)-(−)-2,3-*Dihydro*-2-*isopropyl*-2,5-*dimethylfuran* **1**

(*R*)-**1** (301 mg) obtained in 21.0% yield from (*R*)-**6** showed the following properties: b.p. 54 ~ 56°/78 mm, $[\alpha]_D^{22}$ − 8.6° (c = 0.76, pentane); ν_{max} 3090 (w), 2960 (s), 2920 (sh, s), 2870 (s), 1675 (s), 1460 (sh, m), 1445 (m), 1430 (sh, m), 1375 (s), 1365 (s), 1335 (w), 1315 (m), 1275 (s), 1230 (m), 1185 (s), 1160 (w), 1120 (m), 1110 (m), 1100 (sh), 1080 (m), 1060 (m), 1045 (m), 1023 (m), 1010 (m), 975 (m), 950 (s), 925 (m), 880 (m), 840 (w), 765 (w), 710 (m)cm^{-1}; ^{1}H-NMR δ 0.86 (3H, d, J = 7 Hz), 0.88 (3H, d, J = 7 Hz), 1.17 (3H, s), 1.66 (3H, br s), 1.58 ~ 2.70 (3H, m), 4.33 (1H, br s); ^{13}C-NMR δ (C_6D_6) 13.87, 17.38, 23.81, 37.44, 39.75, 89.27, 93.14, 153.69; GLC–MS (measured on a JMS-DX 300 apparatus): *m/z* 151 (M^+ + 1, 4.5%), 150 (M^+=$C_9H_{16}O$,

39%), 125 (23%), 107 (12%), 98 (11%), 97 (100%, base peak), 96 (9%), 95 (9%), 83 (20%), 82 (14%), 81 (6%), 79 (10%), 71 (21%), 70 (64%), 69 (19%), 67 (14%), 58 (8%), 57 (4.5%), 55 (79%), 54 (6%), 53 (14%), 43 (55%), 42 (20%), 41 (45%), 39 (23%); GLC (column, PEG 20 M, 50 m × 0.25 mm at 90°; carrier gas, N_2, 50 ml/min): R_t 2.1 min (99%), 6.7 min (1%, impurity).

(S)-(−)-5,6-*Dimethyl*-5-*hydroxy*-2-*heptanone* **8**

This was prepared from (*S*)-**6** in the same manner as described above for the preparation of (*R*)-**8**. The optical rotation of chromatographically pure (*S*)-**8** was: $[\alpha]_D^{23} - 5.52°$ (c = 1.03, pentane) or $[\alpha]_D^{23} - 4.86°$ (c = 1.05, $CHCl_3$).

(S)-(+)-2,3-*Dihydro*-2-*isopropyl*-2,5-*dimethylfuran* **1**

This was prepared from (*S*)-**6** (1.05 g) in 26.3% yield (273 mg), b.p. 51 ~ 54°/72 mm, $[\alpha]_D^{22} + 9.3°$ (c = 0.85, pentane); GLC (column, PEG 20 M, 50 m × 0.25 mm at 90°; carrier gas, N_2, 50 ml/min): R_t 2.05 min (99.3%), 6.4 min (0.7%, impurity). The spectral properties were identical with those described for (*R*)-**1**.

(±)-2-*Hydroxy*-2,3-*dimethylbutanenitrile* **10**

A mixture of **9** (200 g) and KCN soln (156 g in 534 ml of H_2O) was stirred and ice-cooled at 8°. 40% H_2SO_4 (454 ml) was added dropwise to a stirred and ice-cooled mixture keeping the reaction temp below 10 ~ 15°. After the addition the mixture was stirred for 30 min and then left to stand for a while. The organic layer was separated and the aq layer was filtered to remove the inorganic material. The filtrate was extracted with ether. The combined organic solution was dried (Na_2SO_4) and concentrated *in vacuo* to give 278 g of crude **10**, ν_{max} 3450 (s), 2240 (w), 1160 (s), 1100 (s) cm^{-1}. This was used in the next step without further purification.

(±)-2-*Hydroxy*-2,3-*dimethylbutanoic acid* **11**

Conc HCl (1000 ml) was added to **10** (278 g) and the mixture was left to stand at room temp for 10 days. It was then heated under reflux for 2 days. Precipitated NH_4Cl was dissolved by the addition of the minimal amount of water and the soln was extracted with ether. The ether soln was dried (Na_2SO_4) and concentrated *in vacuo*. The residual oil crystallized. Recrystallization of crude **11** from C_6H_6–pet ether gave 200 g (65.2% from **9**) of pure (±)-**11**, m.p. 70 ~ 71°, ν_{max} 3450 (s), ~2650 (w), 1730 (s), 1260 (m), 1190 (m), 1165 (m), 1050 (m) cm^{-1}; δ ($CDCl_3$) 0.89 (3H, d, J = 7 Hz), 0.95 (3H, d, J = 7 Hz), 1.41 (3H, s), 1.8 ~ 2.3 (1H, m), 6.55 (2H, br). (Found: C, 54.67; H, 9.03. Calc for $C_6H_{12}O_3$: C, 54.53; H, 9.15%.)

Optical resolution of (±)-**11**

(*S*) - (−) - α - Phenylethylamine (> 99% ee, 95.3 g) was added to a soln of (±)-**11** (104 g) in i-PrOH (300 ml). The separated crystals were collected on a filter. The crude amine salt was pulverized thoroughly and suspended in i-PrOH (130 ml). The suspension was stirred and heated at 40 ~ 45° for 60 ~ 100 min. The insoluble salt was collected on a filter. Pulverization and washing of the salt was repeated four more times. The remaining insoluble salt was recrystallized 6 times from i-PrOH–pet ether to give 8.74 g (8.8%) of the (*S*) - (−) - α - phenylethylamine salt of (+)-**11** as needles, m.p. 142°, $[\alpha]_D^{20} - 8.3°$ (c = 0.98, MeOH); ν_{max} 3440 (m), 2200 (w), 1640 (m), 1550 (s), 1530 (s), 1340 (m), 1035 (m), 755 (m) cm^{-1}. (Found: C, 66.51; H, 9.11; N, 5.53. Calc for $C_{14}H_{23}O_3N$: C, 66.37; H, 9.15; N, 5.53%.) The 1st, 2nd and 3rd filtrates obtained in the course of washing the crude salt with i-PrOH were combined and concentrated *in vacuo* to give a crude salt enriched with (−)-**11**. This was treated with 2N HCl to give a crude acid enriched with (−)-**11** (38 g). To the crude (−)-**11** was added (*R*) - (+) - α - phenylethylamine (35 g). The salt was recrystallized 13 times from i-PrOH or i-PrOH–pet ether to give 9.20 g (9.6%) of the (*R*) - (+) - α - phenylethylamine salt of (−)-**11** as needles, m.p. 144°, $[\alpha]_D^{20} + 8.9°$ (c = 0.98, MeOH). Its IR spectrum was identical to that of the antipode. (Found: C, 66.18; H, 9.00; N, 5.54. Calc for $C_{14}H_{23}O_3N$: C, 66.37; H, 9.15; N, 5.53%.)

The (−)-salt (8.00 g) was dissolved in N HCl (40 ml) and the soln was extracted with ether (50 ml × 4). The ether soln was washed with H_2O and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystallized from pet ether to give 3.86 g (7.4%) of (+)-**11**, m.p. 42 ~ 43°, $[\alpha]_D^{20} + 7.1°$ (c = 1.06, $CHCl_3$) [lit[11] $[\alpha]_D^{20} + 4.57°$ ($CHCl_3$)]; ν_{max} 3450 (s), ~2650 (m), 1730 (s), 1165 (m), 1145 (m) cm^{-1}. Its ^1H-NMR spectrum was identical to that of (±)-**11**. CD (l = 0.03 dm, c = 7.95 × 10^{-3} mol/l, MeOH): λ_{max} 209 nm ($\Delta\epsilon = +88$). (Found: C, 54.38; H, 8.97. Calc for $C_6H_{12}O_3$: C, 54.53; H, 9.15%.) In the same manner, the (+)-salt (8.00 g) gave 3.74 g (7.2%) of (−)-**11**, m.p. 42 ~ 44°; $[\alpha]_D^{20} - 7.1°$ (c = 1.05, $CHCl_3$). The IR and NMR spectra were identical to those of (+)-**11**. CD (l = 0.03 dm, c = 9.47 × 10^{-3} mol/l, MeOH): λ_{max} 209 nm ($\Delta\epsilon = -60$). (Found: C, 54.52; H, 8.83. Calc for $C_6H_{12}O_3$: C, 54.53; H, 9.15%.) By these CD measurements, (+)-**11** was deduced to be (*S*), and (*R*)-configuration was assigned to (−)-**11**.

(S)-(−)-2,3-*Dimethyl*-1,2-*butanediol* **5a**

A soln of (*S*)-(+)-**11** (3.75 g) in dry THF (30 ml) was added dropwise to a stirred and ice-cooled suspension of LAH (2.30 g) in dry THF (150 ml). After the addition, the mixture was stirred and heated under reflux for 3.5 h. It was then ice-cooled and the excess LAH was destroyed by the addition of H_2O (2.3 ml), 10% KOH soln (2.3 ml) and H_2O (6.9 ml). The stirring was continued for 2 h. The mixture was filtered and the filter cake was washed with THF. The combined filtrate and washings were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 2.84 g (85%) of (*S*)-**5a**, b.p. 98 ~ 100.5°/16 mm, n_D^{21} 1.4456; $[\alpha]_D^{21} - 13.4°$ (c = 1.00, $CHCl_3$). The spectral data were identical to those of an authentic sample. (Found: C, 60.70; H, 12.03. Calc for $C_6H_{12}O_2$: C, 60.98; H, 11.94%.)

(R)-(+)-2,3-*Dimethyl*-1,2-*butanediol* **5a**

In the same manner as described above, 3.63 g of (*R*) - (−) - **11** yielded 2.68 g (83%) of (*R*)-**5a**, b.p. 97 ~ 100.5°/14 mm, n_D^{21} 1.4455; $[\alpha]_D^{21} + 13.9°$ (c = 1.02, $CHCl_3$). The spectral data of (*R*)-**5a** were identical to those of (*S*)-**5a**. (Found: C, 60.32; H, 12.04. Calc for $C_6H_{12}O_2$: C, 60.98; H, 11.94%.)

Determination of the optical purity of **5a** *prepared from* **11**

The MTPA ester of (±)-**5a** was prepared in the usual manner using (*S*) - (−) - MTPA. The MTPA ester of (−)-**5a** was prepared employing (*R*) - (+) - MTPA. HPLC was measured on Shimadzu LC-2 apparatus (column, Partisil 5, 25 cm × 4.6 mm; eluent, n-hexane–ether 20:1; pressure, 30 kg/cm^2; detector, 254 nm): R_t 45.0 min [(*S*) - (−) - **5a**·(*S*) - (−) - MTPA ester], 47.8 min [(*R*) - (+) - **5a**·(*S*)-(−) - MTPA ester]. In another run under the same conditions, (*S*) - (−) - **5a**·(*R*) - (+) - MTPA ester showed a single peak at R_t 46.8 min. Optical purity of (*S*) - (−) - **5a** = ~100%.

(3R)-(−)-3,7-*Dimethyl*-1,2-*epoxy*-6-*octen*-3-*ol* **12**

The optical purity of (*R*) - (−) - linalool **3** employed in this work was estimated to be 92.4% basing on its specific rotation: $[\alpha]_D^{23} - 17.94°$ (c = 8.19, $CHCl_3$). Optically pure **3** was reported to show $[\alpha]_D^{20} - 19.42°$ (c = 8.15, $CHCl_3$).[16] Commercially available 70% t-BuOOH (18.2 g) was added dropwise during 20 min to a stirred and heated soln of (*R*)-**3** (20 g) and $VO(acac)_2$ (500 mg) in C_6H_6 (150 ml) under reflux. The mixture was stirred and heated under reflux for 14 h and cooled. It was then washed with $NaHSO_3$ soln, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Merck Kieselgel 60, 400 g). Elution with n-hexane–ether (10:1 ~ 3:1) gave **12**. This was distilled to give 11.5 g (52%) of pure **12**, b.p. 76 ~ 77.5°/4 mm, n_D^{21}

1.4590; $[\alpha]_D^{21} - 11.1°$ (c = 1.26, $CHCl_3$); ν_{max} 3450 (br s), 1110 (m), 910 (m), 865 (m) cm^{-1}; δ 1.09 and 1.21 (s each, total 3H), 1.3 ~ 1.8 (2H, m), 1.60 (6H, br s), 1.8 ~ 2.35 (2H, m), 2.13 (1H, s), 2.45 ~ 2.95 (3H, m), 5.08 (1H, t, J = 7 Hz). (Found: C, 70.08; H, 10.58. Calc for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66%.)

(3R)-(−)-3,7-*Dimethyl-6-octene*-2,3-*diol* **13a**

A soln of **12** (5.38 g) in dry ether (100 ml) was added dropwise to a stirred and ice-cooled suspension of LAH (1.2 g) in dry ether (50 ml). The mixture was stirred overnight at room temp. The excess LAH was destroyed by the successive addition of H_2O (1.2 ml), 2N NaOH (2.4 ml) and H_2O (1.2 ml) to the stirred and ice-cooled mixture. After stirring for 1.5 h, anhyd $MgSO_4$ was added to the mixture. It was then filtered and the filter cake was washed thoroughly with THF. The combined filtrate and washings were concentrated *in vacuo*. The residue was distilled to give 4.96 g (91.2%) of **13a**, b.p. 95 ~ 96.5°/0.4 mm, $n_D^{21.5}$ 1.4662; $[\alpha]_D^{22} - 1.34°$ (c = 1.19, $CHCl_3$); ν_{max} 3400 (br s), 1085 (s), 1070 (s) cm^{-1}; δ 0.9 ~ 1.3 (6H, m), 1.3 ~ 2.5 (12H, m), 3.0 ~ 3.2 (1H), 3.3 ~ 3.8 (2H, m), 5.09 (1H, t, J = 7 Hz). (Found: 69.65; H, 11.68. Calc for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70%.)

(3R)-3,7-*Dimethyl*-2-*tosyloxy*-6-*octen*-3-*ol* **13b**

p-TsCl (6.90 g) was added to a stirred and ice-cooled soln of **13a** (4.75 g) in dry C_5H_5N (20 ml). The stirring was continued overnight at 5°. The mixture was diluted with ether (50 ml) and poured into iced-dil HCl. The organic layer was separated and the aq layer was extracted with ether. The combined organic soln was washed with dil HCl and $CuSO_4$ soln, dried ($MgSO_4$) and concentrated *in vacuo* to give 9.80 g of crude **13b**, ν_{max} 3450 (m), 1600 (m), 1375 (s), 1190 (s), 1175 (s), 910 (s) cm^{-1}. This was employed in the next step without further purification.

(R)-(−)-2,3,7-*Trimethyl*-6-*octen*-3-*ol* **14**

A soln of MeLi in ether (1.30 N, 53 ml) was added to a stirred and cooled suspension of CuCN (6.18 g) in dry ether (50 ml) at −65° under Ar. The heterogeneous mixture was allowed to warm to 0°, stirred for several min at that temp, and recooled to −65°. To this was added a soln of **13b** (9.80 g) in dry ether (20 ml). The reaction temp was raised to room temp. After stirring for 7 h, the mixture was poured into NH_3 aq (10 ml) and sat NH_4Cl soln (90 ml). This was stirred for 30 min and filtered to remove insoluble material. The filtrate was extracted with ether. The ether soln was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Merck Kieselgel 60, 130 g). Elution with n-hexane–ether (20:1 ~ 10:1) gave **14**. This was distilled to give 3.75 g (80.0%) of pure **14**, b.p. 97 ~ 98°/22 mn, n_D^{22} 1.4537; $[\alpha]_D^{21} - 4.0°$ (c = 1.05, $CHCl_3$); ν_{max} 3440 (br, m), 1180 (m), 1115 (m), 1085 (m), 915 (m) cm^{-1}; δ 0.86 (3H, d, J = 7 Hz), 0.90 (3H, d, J = 7 Hz), 1.02 (3H, s), 1.61 (3H, br s), 1.67 (3H, br s), 1.2 ~ 2.4 (6H, m), 5.10 (3H, t, J = 7 Hz). (Found: C, 77.36; H, 12.92. Calc for $C_{11}H_{22}O$: C, 77.58; H, 13.02%.)

(R)-(−)-4,5-*Dimethyl*-4-*hexanolide* **15**

$NaIO_4$ (9.96 g) was added to a biphasic soln of **14** (1.93 g) in CCl_4 (23 ml), MeCN (23 ml) and H_2O (34 ml). After stirring for 5 min, $RuCl_3 \cdot 3H_2O$ (56.4 mg) was added to the mixture. It was stirred vigorously for 23 h at room temp. Then CH_2Cl_2 (100 ml) was added, and the organic layer was separated. The aq layer was extracted with CH_2Cl_2. The combined organic soln was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was diluted with ether (200 ml), filtered through Celite and concentrated. The residue was chromatographed over SiO_2 (Merck Kieselgel 60, 60 g). Elution with n-hexane–ether (20:1 ~ 8:1) gave **15**. This was distilled to give 1.29 g (80.1%) of pure **15**, b.p. 114 ~ 116°/21 mm, n_D^{21} 1.4433; $[\alpha]_D^{21} - 10.2°$ (c = 1.07, $CHCl_3$); ν_{max} 1765 (s), 1255 (m), 1240 (m), 1205 (m), 1170 (m), 1085 (m), 930 (m) cm^{-1}; δ 0.92 (3H, d, J = 7 Hz), 0.97 (3H, d, J = 7 Hz), 1.28 (3H, s), 1.6 ~ 2.7 (5H, m). (Found: C, 67.30; H, 9.85. Calc for $C_8H_{14}O_2$: C, 67.57; H, 9.93%.)

(R)-(−)-2,3-*Dihydro*-2-*isopropyl*-2,5-*dimethylfuran* **1**

LiOH aq soln (20%, 15 ml) was added to a soln of **15** (760 mg) in MeOH (7 ml) and the mixture was heated under reflux for 1.5 h. After cooling, the mixture was extracted with ether. The aq layer was concentrated *in vacuo*. The residue was dissolved in MeOH (10 ml) and filtered to remove the insoluble material. The filtrate was concentrated *in vacuo* and the residue was dried over P_2O_5. It was then suspended in DME (8 ml). A soln of MeLi in ether (0.68 N, 18.1 ml) was added to this suspension with stirring and cooling (−20°) under Ar. The mixture was stirred for 1.5 h at room temp and poured into sat NH_4Cl soln. The organic layer was separated and the aq layer was extracted with ether. The combined organic soln was washed with brine, dried ($MgSO_4$) and concentrated under atmospheric pressure with a Vigreux column. The residue [(*R*)-**8**] was distilled in the presence of $CaSO_4$ to give 65 mg (10.1%) of pure (*R*)-**1**, $[\alpha]_D^{24} - 8.1°$ (c = 0.51, pentane); GLC (column, OV-101, 30 m × 0.3 mm at 50°; carrier gas, N_2, 50 ml/min): R_t 2.0 min (94.4%), 6.6 min (4.2%, impurity), 7.6 min (1.4%, impurity). This sample showed the IR spectrum identical to that of an authentic sample.

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