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Mammalian blood odorant and chirality: synthesis and sensory evaluation by humans and mice of the racemate and enantiomers of *trans*-4,5-epoxy-(*E*)-2-decenal

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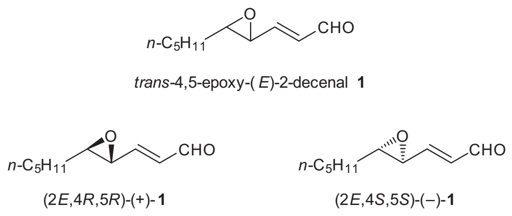
ABSTRACT

The racemate and enantiomers of *trans*-4,5-epoxy-(*E*)-2-decenal **1**, an odorant with a metallic blood smell, were synthesized. The detection threshold for humans was 0.019 ppb for (2*E*,4*S*,5*S*)-(−)-**1** and 0.62 ppb for (2*E*,4*R*,5*R*)-(+)-**1**, respectively. The racemate (±)-**1** made mice scared stiff at a dosage of approximately 1 mg, while the enantiomers were not significantly bioactive.

1. Introduction

In 2014, Nilsson et al. reported that *trans*-4,5-epoxy-(*E*)-2-decenal **1** (Fig. 1) could be as efficient in eliciting behavioral responses among dogs and tigers as the odor of mammalian blood.[1] The fact that the metallic blood smell of **1** attracts predators is of interest in its ecological context to study the chemistry of how carnivores find their prey.[2] Nilsson et al., however, examined only racemic **1**, which had been known since 1991 as one of the primary odorants in wheat bread crumb[3] and popcorn[4] by Schieberle et al. Aldehyde **1** was found in many other food systems[5] such as black tea,[6] and its biogenetic pathway was speculated.[7]

There are two reports, which describe the preparation of optically active **1**. Zamboni et al. prepared (2*E*,4*S*,5*S*)-**1** from 2-deoxy-D-ribose as an intermediate in the course of their leukotriene synthesis, although they did not describe its physical data including the specific rotation.[8] In the patent literature, Daniher et al. described the synthesis of both (+)- and (−)-**1** by Jacobsen's asymmetric epoxidation, and assigned the absolute configuration of (−)-**1** as (4*S*,5*S*) by converting it into a compound reported by Zamboni.[9]


trans-4,5-epoxy-(*E*)-2-decenal **1**

(2*E*,4*R*,5*R*)-(+)-**1**

(2*E*,4*S*,5*S*)-(−)-**1**

Figure 1. Structure of *trans*-4,5-epoxy-(*E*)-2-decenal **1**.

We became interested in synthesizing the racemate as well as the enantiomers of **1** with known absolute configuration and enantiomeric purity so as to compare their odorant properties. Herein we report a scalable and efficient synthesis of (±)-, (2*E*,4*R*,5*R*)-(+)- and (2*E*,4*S*,5*S*)-(−)-**1**, together with the preliminary results of their sensory evaluation by humans and mice. It was shown that to the human nose (2*E*,4*S*,5*S*)-(−)-**1** smelled about twenty to thirty times more intensive than its enantiomer. Mice were scared stiff when approximately 1 mg of (±)-**1** was released.

2. Results and discussion

2.1. Synthesis of racemic *trans*-4,5-epoxy-(*E*)-2-decenal 1

Prior to the synthesis of the enantiomers of **1**, that of the racemate was examined as shown in Scheme 1 so as to find a scalable route, which was needed, because a multi-gram amount of **1** was necessary to carry out mammalian sensory evaluation of **1** against mice and deer. Schieberle's route was first examined with regard to its efficiency. This protocol involved epoxidation of commercially available (2*E*,4*E*)-2,4-decadienal **2**.[3] In our hands, however, epoxidation of **2** with *m*-chloroperbenzoic acid in CH_2Cl_2 gave impure

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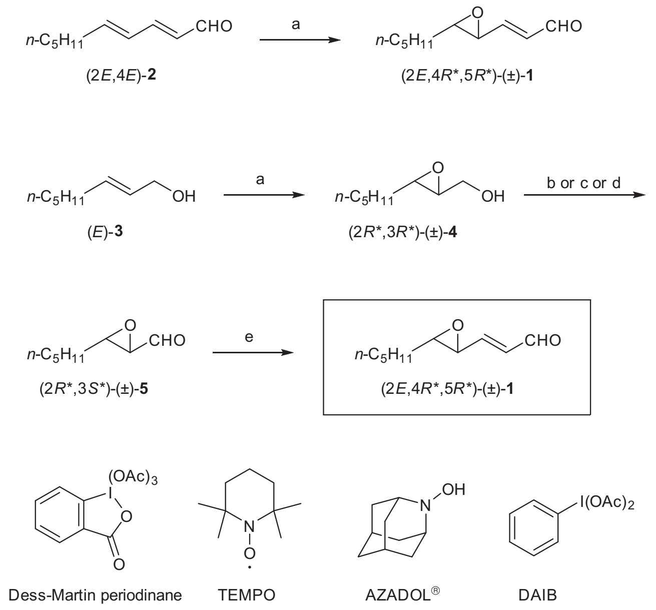


Scheme 1. Synthesis of (±)-**1**. Reagents and conditions: (a) *m*-chloroperbenzoic acid, CH_2Cl_2 [3% for (±)-**1**; 94% for (±)-**4**]: (b) Dess–Martin periodinane, CH_2Cl_2 (62%); (c) TEMPO, DAIB, CH_2Cl_2 (80%); (d) AZADOL,® DAIB, CH_2Cl_2 (78%); (e) $Ph_3P{=}CHCHO$, C_6H_6 (87%).

(±)-**1** in a very low yield of 3% after chromatographic purification on SiO_2.

The next attempt was to convert commercially available (*E*)-2-octen-1-ol **3** into (±)-**1**, hoping to improve the efficiency of the previous results.[5,7,10,11] Epoxidation of **3** with *m*-chloroperbenzoic acid in CH_2Cl_2 gave epoxy alcohol (±)-**4** in a satisfactory yield of 94% after distillation. It should be noted that this step can be modified to give either (+)- or (−)-**4** by employing an asymmetric epoxidation developed by Katsuki and Sharpless.[12,13]

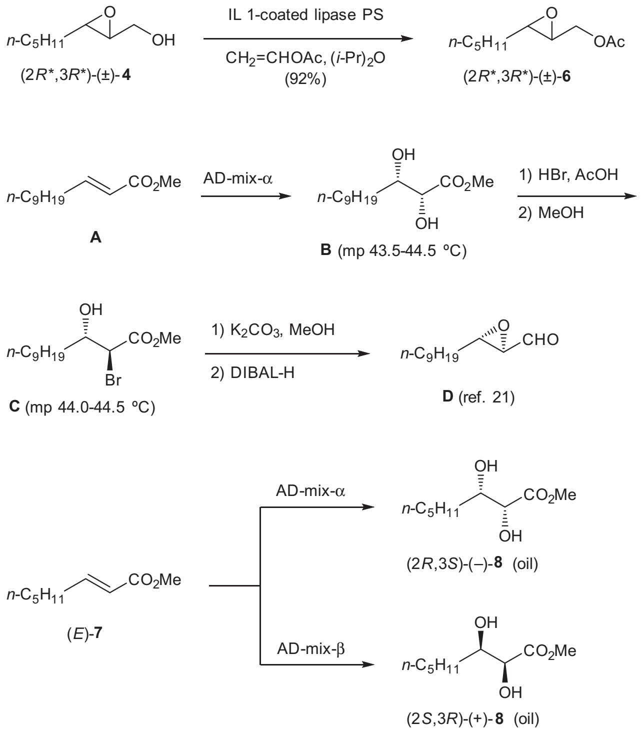
Although Swern oxidation of (±)-**4** failed to give aldehyde (±)-**5** under standard conditions [DMSO/$(COCl)_2$ and Et_3N], Dess–Martin periodinane[14] in CH_2Cl_2 cleanly converted (±)-**4** into (±)-**5** in 62% yield. Since the oxidation of the enantiomers of **4** with 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) and (diacetoxyiodo)benzene (DAIB) in CH_2Cl_2 was recently published by Rizzo et al.,[15] the TEMPO/DAIB oxidation of (±)-**4** was carried out to give (±)-**5** as a slightly pink-colored oil in 80% yield after chromatographic purification and distillation. Iwabuchi's highly active 2-azaadamantan-*N*-oxyl (AZADO) catalyst[16] was then used for the oxidation. Only 1.6 mol % of AZADOL® (2-hydroxyo-2-aza-adamantane) catalyzed the oxidation of (±)-**4** into (±)-**5** within 1 h to give (±)-**5** as a colorless oil in 78% yield, while oxidation of (±)-**4** in the presence of 17 mol% of TEMPO required 3.5 h for completion. AZADOL®/DAIB oxidation was therefore adopted for the multi-gram scale preparation of (±)-**5**.

Two-carbon elongation of (±)-**5** to give (±)-**1** was carried out by a Wittig reaction between (±)-**5** and commercially available (triphyenylphosphoranylidene)acetaldehyde in C_6H_6. After chromatographic purification and distillation, the desired (±)-*trans*-4,5-epoxy-(*E*)-2-decenal **1** was obtained in 87% yield as a colorless and odoriferous oil. Its ^1H NMR, ^{13}C NMR and MS spectra were in good accord with those previously reported.[3,5] The overall yield of (±)-**1** was 65% based on **3** (three steps). The procedure reported in Section 4 is highly reproducible, and over 10 g of (±)-**1** could be secured for sensory evaluation against mice and deer. The present method is the most efficient one for the preparation of (±)-**1**.

2.2. Synthesis of the enantiomers of *trans*-4,5-epoxy-(*E*)-2-decenal 1

2.2.1. Attempted asymmetric acetylation of (±)-*trans*-2,3-epoxy-1-octanol 4

Since epoxy alcohol (±)-**4** was readily available, we first attempted its asymmetric acetylation with vinyl acetate in the presence of lipase PS, which has been employed widely to prepare enantiopure building blocks.[17] Lipase PS was a remarkably suitable enzyme to give (2*S*,3*R*)-4-*t*-butyldimethylsilyloxy-2,3-epoxybutyl acetate (98% ee) from the corresponding racemic alcohol by enzymatic asymmetric acetylation with vinyl acetate.[18] In the present case with (±)-**4** however, lipase PS coated with an ionic liquid [IL 1:α-cetylpolyoxyethylene(19)ether sulfate][19] could not discriminate the enantiomers of **4**, and after only 4 h at room temperature, (±)-**4** furnished the corresponding racemic acetate (±)-**6** in 95% yield (Scheme 2). The enzymatic route was therefore abandoned.



Scheme 2. Attempted routes for the synthesis of optically active **1**.

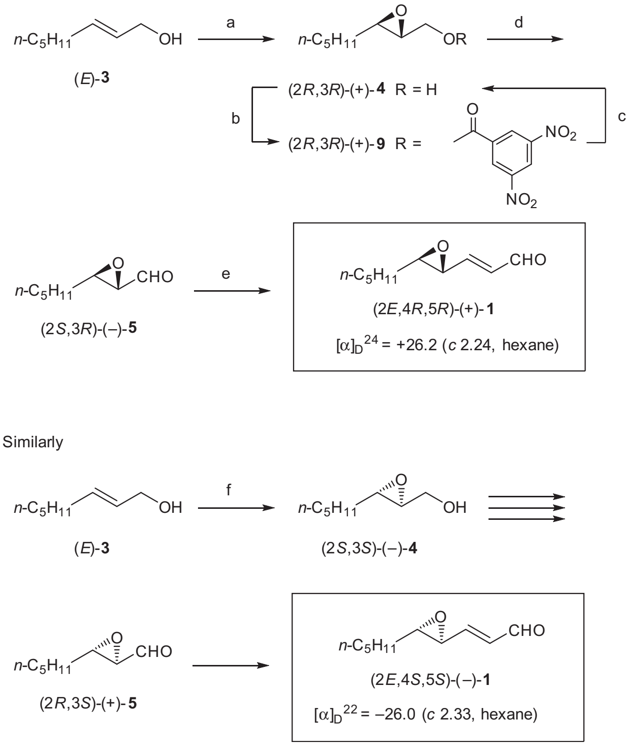
2.2.2. Attempted AD (asymmetric dihydroxylation)-mediated route

Asymmetric dihydroxylation (AD) as developed by Sharpless et al. is one of the most versatile enantioselective methods in organic synthesis.[20] In 2001 we applied AD in our pheromone synthesis, converting α,β-unsaturated ester **A** into enantiopure aldehyde **D**.[21] This was possible because both dihydroxy ester **B** and bromohydrin ester **C** were nicely crystalline. Their purification was possible by recrystallization.

The AD of methyl (*E*)-2-octenoate **7** with either AD-mix-α® or AD-mix-β® gave (2*R*,3*S*)- or (2*S*,3*R*)-**8**, respectively, both as oils. Since recrystallization of **8** was impossible, we gave up this approach, and came back to the more traditional endeavor to use the Sharpless asymmetric epoxidation for the preparation of the enantiomers of **4**.

2.2.3. Asymmetric epoxidation-mediated synthesis of the enantiomers of 1

In 1980, Katsuki and Sharpless invented asymmetric epoxidation.[12] Since then asymmetric epoxidation has been widely used in organic synthesis.[13] Indeed, the asymmetric epoxidation of (*E*)-2-octen-1-ol **3** (Scheme 3) was repeatedly reported to give the enantiomers of **4**.[13,22,23] With regard to the experimental procedure for the conversion of **3** into (+)-**4** or (−)-**4**, we adopted Taber's protocol for the asymmetric epoxidation of geraniol, avoiding chromatographic purification.[24]



Scheme 3. Synthesis of the enantiomers of **1**. Reagents and conditions: (a) *t*-BuOOH, Ti(O*i*-Pr)$_4$, (−)-DET, MS 4 Å, CH_2Cl_2, -20 °C, 6 h (88%); (b) 3,5-dinitrobenzoyl chloride, DMAP, C_5H_5N, Et_2O; recryst'n (58%); (c) K_2CO_3, MeOH, THF, 0–5 °C, 1 h (95%); (d) Dess–Martin periodinane, CH_2Cl_2 (66%); (e) $Ph_3P{=}CHCHO$, C_6H_6 (86%); (f) *t*-BuOOH, Ti(O*i*-Pr)$_4$, (+)-DET, MS 4 Å, CH_2Cl_2, −20 °C, 6 h (81%).

The asymmetric epoxidation of **3** with *t*-BuOOH, Ti(O*i*-Pr)$_4$ and diethyl (2*S*,3*S*)-(−)-tartrate [(−)-DET] in the presence of powdered MS 4 Å in CH_2Cl_2 at −20 °C for 6 h afforded (2*R*,3*R*)-(+)-**4** in 88% yield after work-up and distillation. Its specific rotation, $[\alpha]_D^{18} = +34.5$ (*c* 5.56, $CHCl_3$), was consistent with the reported value of $[\alpha]_D^{27} = +38.6$ (*c* 1.0, $CHCl_3$).[22] Similarly, by employing diethyl (2*R*,3*R*)-(+)-tartrate [(+)-DET] instead of (−)-DET, (2*S*,3*S*)-(−)-**4** was obtained in 81% yield, $[\alpha]_D^{22} = -36.1$ (*c* 4.39, $CHCl_3$) {Ref. 23. $[\alpha]_D^{22} = -34.6$ (*c* 5.7, $CHCl_3$)}.

In order to increase the enantiomeric purities of the enantiomers of **4**, they were converted into the corresponding 3,5-dinitrobenzoates (3,5-DNB esters), which were crystalline.[cf.25] Two recrystallizations afforded (2*R*,3*R*)-(+)-**9** {mp 50.5–51.0 °C; $[\alpha]_D^{22} = +34.5$ (*c* 3.38, $CHCl_3$)} and (2*S*,3*S*)-(−)-**9**{mp 50 °C; $[\alpha]_D^{21} = -34.9$ (*c* 3.80, $CHCl_3$)}. These enantiomers of **9** were shown to be of ca. 95% ee by enantioselective HPLC analysis on Chiralpak® AD-H (see Section 4). Methanolysis of the crystalline enantiomers of **9** with K_2CO_3/MeOH gave back (2*R*,3*R*)-(+)-**4** {$[\alpha]_D^{23} = +33.4$ (*c* 4.59, $CHCl_3$); 96.2% ee as determined by enantioselective GC analysis on heptakis (2,3-di-*O*-acetyl-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin (see Section 4)} and (2*S*,3*S*)-(−)-**4**{$[\alpha]_D^{21} = -34.5$ (*c* 4.50, $CHCl_3$); 95.8% ee}, respectively.

Subsequent Dess–Martin periodinane oxidation of (2*R*,3*R*)-(+)-**4** gave aldehyde (2*S*,3*R*)-(−)-**5**, $[\alpha]_D^{23} = -93.4$ (*c* 1.21, pentane) {Ref. 15. $[\alpha]_D^{25.7} = -98.6$ (*c* 0.35, $CHCl_3$)}. Similarly, (2*S*,3*S*)-(−)-**4** was oxidized with Dess–Martin periodinane to give (2*R*,3*S*)-(+)-**5**, $[\alpha]_D^{21} = +93.2$ (*c* 1.40, pentane){Ref. 15 $[\alpha]_D^{24.7} = +98.3$ (*c* 0.48, $CHCl_3$)}.

Finally, two-carbon elongation of the enantiomers of **5** was carried out with $Ph_3P{=}CHCHO$ in C_6H_6. Accordingly, (2*S*,3*R*)-(−)-**4** was subjected to the Wittig reaction to give (4*R*,5*R*)-(+)-**1**, $[\alpha]_D^{24} = +26.2$ (*c* 2.24, hexane), while (2*R*,3*S*)-(+)-**4** furnished (4*S*,5*S*)-(−)-**1**, $[\alpha]_D^{22} = -26.0$ (*c* 2.33, hexane). Their IR, ^{1}H and^{13}C NMR, and MS spectra were identical with those of (±)-**1**. Their enantiomeric purities were determined by enantioselective GC on a Chiramix® column,[26] and found to be 97.2% ee for (4*R*,5*R*)-(+)-**1** and 96.2% ee for (4*S*,5*S*)-(−)-**1**. The overall yield of (+)-**1** was 26% and that of (−)-**1** was 24% based on **3** (five steps including the enrichment steps). Both enantiomers of *trans*-4,5-epoxy-(*E*)-2-decenal **1** were secured in quantities sufficient for their sensory evaluation.

2.3. Sensory evaluation of the racemate and enantiomers of *trans*-4,5-epoxy-(*E*)-2-decenal 1

2.3.1. By humans

The odors of the synthetic (2*E*,4*R*,5*R*)-(+)-**1**, (±)-**1** and (2*E*,4*S*,5*S*)-(−)-**1** were examined by dissolving trace amounts of each of the samples into water, and their recognition threshold as well as detection threshold were determined by a group (22–26 persons) of flavor scientists at T. Hasegawa Co. The results are shown in Table 1.

Table 1
Recognition and detection thresholds of (+)-, (±)- and (−)-**1** as determined by a panel of flavor scientists

Sample	Recognition threshold (ppb)	Detection threshold (ppb)	Number of panelists
(2*E*,4*R*,5*R*)-(+)-**1**	1.1	0.62	22
(±)-**1**	0.20	0.073	24
(2*E*,4*S*,5*S*)-(−)-**1**	0.047	0.019	26

It should be noted that (−)-**1** was twenty to thirty times more intensive odorant than (+)-**1**. People at Givaudan Co. also noticed that the odor of (−)-**1** was at least ten times stronger than (+)-**1**.[9] Their enantiomers of **1** were prepared by Jacobsen's asymmetric epoxidation.[27]

Impressions of the odors of (+)- and (−)-**1** as 0.01% solution in triacetin (triacetylglycerol) were examined by flavorists at T. Hasegawa Co. Their responses were as follows:—(+)-**1**: weak, metallic, green and oily, and (−)-**1**: strong, metallic, oily, fatty and peely. Both enantiomers of **1** showed similar odor quality, although they were different in odor intensity.

2.3.2. By mice

The effects of (+)-, (−)- and (±)-*trans*-4,5-epoxy-(*E*)-2-decenal **1** on mice were examined by behavioral observation at Health Science University of Hokkaido. Fear induction among mice caused by blood odor seems to be the result of an instinctive memory that conveys information about predation and injury. To assess the behavioral responses of mice to the enantiomers and racemate of **1**, a test for freezing (i.e., immobilization) was performed with the synthetic samples released for 5 min.[28]

Three-month-old female C57BL/6j mice[29] ($n = 24$) were used in the present experiment. One μL (=ca. 1 mg) of either (+)- or (−)-**1** tended to increase the freezing duration, but not so significant. On the other hand, 1 μL (=ca. 1 mg) of (±)-**1** evoked significantly longer freezing duration: 53.2 ± 8.5 s, $P < 0.01$ vs. control 16.2 ± 3.4 s. ANOVA followed by Dunnett's post-hoc test.[30]

These results clearly indicate that blood must produce a mixture of the enantiomers of **1**, if mice are to communicate the fear situation with each other. Synergistic response to enantiomers was first discovered in 1976 in the case of an insect aggregation pheromone sulcatol(6-methyl-5-hepten-2-ol).[31] Further studies are currently in progress to clarify the enantiomeric composition of **1** derived from mammalian blood, and the results will be published in due course by Osada et al. It should be added that people at T. Hasegawa Co. already found that **1**, generated by heating a mixture of beef oil and water, was an almost racemic mixture of (+)-**1** (55.9%) and (−)-**1** (44.1%) as determined by GC–MS analysis on a Chiramix® column.[32]

3. Conclusion

An efficient and scalable synthesis of (±)-*trans*-4,5-epoxy-(*E*)-2-decenal **1** was developed. The enantiomers of **1** were synthesized by employing Sharpless asymmetric epoxidation as the source of chirality. (2*E*,4*S*,5*S*)-(−)-**1** was a twenty to thirty times more intense odorant for humans than (2*E*,4*R*,5*R*)-(+)-**1**, although their odor quality as metallic and oily was similar to each other. The odor of (±)-**1** made mice scared stiff.

4. Experimental[33]

4.1. General

Melting points are uncorrected values. Refractive indices were measured on an Atago DMT-1 refractometer. Optical rotations were measured on a Jasco P-1020 polarimeter. IR spectra were measured on a Jasco FT/IR-410 spectrometer. ^{1}H NMR spectra (400 MHz, TMS at δ = 0.00 as the internal standard) and ^{13}C NMR spectra (100 MHz, $CDCl_3$ at δ = 77.0 as the internal standard) were recorded on a Jeol JNM-AL 400 or JNM-ECZ 400S/L1 spectrometer. GC-MS were measured on Agilent Technologies 5975 inert XL. HRMS were recorded on Jeol JMS-SX 102A, Waters Synapt G2 HDMS, or Varian 901-MS Ion Spec QFT-7. Column chromatography was carried out on Merck Kieselgel 60 Art 1.07734.

4.2. (2*E*,4*R**,5*R**)-(±)-4,5-Epoxy-2-decenal 1 by epoxidation of (2*E*,4*E*)-2,4-decadienal 2

m-Chloroperbenzoic acid (70% purity, 4.16 g, 170 mmol) was added portionwise to an ice-cooled and stirred solution of **2** (2.28 g, 150 mmol) in CH_2Cl_2 (35 mL) at 0–5 °C. The mixture was stirred for 3 h at 0–5 °C, after which it was diluted with hexane, and filtered to remove MCBA. The filter cake was washed with hexane. The combined organic solution was washed with Na_2CO_3 solution containing a small amount of $Na_2S_2O_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo. The residual oil (2.53 g) was chromatographed over SiO_2 (30 g). Elution with hexane/EtOAc (50:1) gave 0.25 g (11%) of recovered **2**. Further elution with hexane/EtOAc (30:1) gave 80 mg (3%) of (2*E*,4*R**,5*R**)-(±)-**1**. Its IR, ^{1}H NMR and MS spectra were identical with those described for (±)-**1** in Section 4.5. Further elution with hexane/EtOAc (10:1–4:1) gave 1.09 g of unidentified polar materials.

4.3. (2*R**,3*R**)-(±)-2,3-Epoxy-1-octanol 4

m-Chloroperbenzoic acid (70% purity, 18.3 g, 75 mmol) was added portionwise to a stirred and ice-cooled solution of **3** (8.5 g, 66.4 mmol) in CH_2Cl_2 (100 mL) at 0–10 °C. The mixture was stirred for 2 h at 0–5 °C, then diluted with hexane, and filtered. The filter cake was washed with hexane. The combined organic solution was washed successively with Na_2CO_3 solution containing a small amount of $Na_2S_2O_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue (10.2 g) was distilled to give 9.02 g (94%) of (2*R**,3*R**)-(±)-**4** as a colorless oil, bp 75–77 °C/2 Torr; n_D^{18} = 1.4412; ν_{max} (film): 3420 (br m), 2957 (s), 2930 (s), 2860 (s), 1467 (m), 1073 (m), 1031 (m), 888 (m); δ_H ($CDCl_3$): 0.90 (3H, t, *J* 6.8), 1.25–1.40 (4H, m), 1.40–1.50 (2H,m), 1.55–1.59 (2H, m), 2.17 (1H, br), 2.90–2.98 (2H, m), 3.61 (1H, d, *J* 12), 3.91 (1H, d, *J* 12); GC–MS [column: HP-5MS, 5% phenylmethylsiloxane, 0.25 mm i.d. × 30 m; carrier gas, He; press 60.7 kPa; temp 70–230 °C (+10 °C/min)]: t_R 7.88 min (97.2%); MS (70 eV, EI): *m*/*z*: 101 (9), 83 (92), 55 (100), 41 (51). HRMS calcd for $C_8H_{17}O_2$ [$(C_8H_{16}O_2+H)^+$]: 145.1229, found: 145.1229.

4.4. (2*R**,3*S**)-(±)-2,3-Epoxyoctanal 5

4.4.1. By Dess–Martin periodinane oxidation of (±)-4

Dess–Martin periodinane (6.00 g, 14 mmol) was added portionwise to a stirred and ice-cooled solution of (±)-**4** (1.50 g, 10.4 mmol) in CH_2Cl_2 (75 mL) containing five drops of water. The mixture was stirred for 20 min at 0–5 °C and then for 1 h at room temperature. Colorless precipitates of *o*-iodobenzoic acid were generated. It was then ice-cooled, and the reaction was quenched by adding $NaHCO_3$ solution. After stirring for 10 min, the mixture was extracted with Et_2O. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was diluted with hexane, and transferred onto a column of SiO_2 (15 g) in hexane. Elution with hexane/EtOAc (20:1) gave 918 mg (62%) of (2*R**,3*S**)-(±)-**5**, n_D^{20} = 1.4358; ν_{max} (film): 2958 (s), 2932 (s), 2860 (s), 2734 (w), 1731 (s), 1467 (m), 1437 (m), 1380 (w), 1241 (w), 1151 (w), 1060 (w), 981 (w), 852 (m), 727 (w); δ_H($CDCl_3$): 0.90 (3H, t, *J* 7.2), 1.30-1.40 (4H, m), 1.42-1.54 (2H, m), 1.60-1.72 (2H, m), 3.14 (1H, dd, *J* 2, 6.4), 3.22 (1H, dt, *J* 2, 6), 9.01 (1H, d, *J* 6); δ_C ($CDCl_3$): 13.87, 22.42, 25.40, 31.12, 31.32, 56.75, 59.11, 198.51; GC–MS (same conditions as those for **4**): t_R 6.58 min (93.5%); MS (70 eV, EI): *m*/*z*: 141 (<1) [$(M-H)^+$], 95 (7), 71 (100), 57 (12), 55 (14), 41 (25). HRMS calcd for $C_8H_{14}O_2$: 142.0994, found: 142.1002.

4.4.2. By TEMPO/DAIB oxidation of (±)-4

At first, DAIB (20.6 g, 64 mmol) was added to a stirred solution of (±)-**4** (8.40 g, 58 mmol) and TEMPO (1.56 g, 10 mmol) in dry CH_2Cl_2 (125 mL). The red solution was stirred for 3.5 h at room temperature. The reaction was slightly exothermic. It was then diluted with CH_2Cl_2 (100 mL) and stirred with 5% $Na_2S_2O_3$ solution (100 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined CH_2Cl_2 solution was washed successively with $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over SiO_2 (100 g). Elution with hexane gave 12.9 g (99% recovery) of C_6H_5I. Further elution with hexane/EtOAc (20:1) gave 8.94 g of crude (±)-**5**. This was purified by distillation to give (2*R**,3*S**)-(±)-**5** (6.64 g, 80%) as a slightly pink-colored oil, bp 57–58 °C/3 Torr; n_D^{18} = 1.4375; GC–MS (same conditions as those for **4**); t_R 6.42 min (88.5%). Its IR, ^{1}H NMR and MS spectra were consistent with those of (±)-**5** prepared by Dess–Martin periodinane oxidation. This was employed in the next step without further purification.

4.4.3. By AZADOL®/DAIB oxidation of (±)-4

At first, DAIB (22.5 g, 70 mmol) was added to a stirred solution of (±)-**4** (9.2 g, 63.9 mmol) and AZADOL® (153 mg, 1 mmol) in dry CH_2Cl_2 (125 mL). The reaction was slightly exothermic, and the temperature of the pale orange-colored solution reached 22 °C. After stirring for 1 h, the mixture was transferred into a separatory funnel, washed successively with $NaHCO_3$ solution containing a small amount of $Na_2S_2O_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo. The residual colorless oil (26.9 g) was chromatographed over SiO_2 (100 g). Elution with hexane gave C_6H_5I (12.8 g). Further elution with hexane/EtOAc (20:1) furnished crude (±)-**5** (8.76 g). This was distilled to give pure ($2R^*$,$3S^*$)-(±)-**5** (7.11 g, 78%) as a colorless oil, bp 56–57 °C/3 Torr; n_D^{23} = 1.4348; GC–MS (column temp 40–230 °C, +5 °C/min; press, 48.7 kPa): t_R 13.24 min (98.3%). Its IR, ^1H NMR and MS spectra were identical with those of (±)-**5** prepared by Dess–Martin periodinane oxidation.

4.5. ($2E$,$4R^*$,$5R^*$)-(±)-4,5-Epoxy-2-decenal 1

Solid $Ph_3P{=}CHCHO$ (TCI, T 2001, 16.7 g, 55 mmol) was added to a solution of (±)-**5** (7.10 g, 50 mmol; prepared by AZADOL®/DAIB oxidation) in dry C_6H_6 (100 mL). The mixture was stirred and heated at 60 °C for 30 min under argon. The initial suspension of the Wittig reagent in the solution of (±)-**5** became a homogeneous and slightly brown-colored solution at the end of this period. It was then left to stand overnight at room temperature under argon. Subsequently, the solution was concentrated in vacuo to give an oily residue, which was mixed with chromatographic SiO_2 (20 g) and hexane. The resulting slurry was placed on the top of a silica gel column (80 g of SiO_2 in hexane) for chromatography. Elution with hexane/EtOAc (20:1) gave 8.65 g of crude (±)-**1**, which was distilled to give 7.32 g (87%) of ($2E$,$4R^*$,$5R^*$)-(±)-**1** as a pale yellow oil, bp 95–96 °C/3 Torr, n_D^{23} = 1.4750; ν_{max} (film): 2958 (s), 2931 (s), 2859 (s), 2729 (w), 1689 (vs), 1639 (m), 1467 (m), 1164 (m), 1122 (m), 1103 (s), 975 (s), 881 (s), 822 (w), 604 (m); δ_H ($CDCl_3$): 0.91 (3H, t, J 6.8), 1.22–1.40 (4H, m), 1.40–1.56 (2H, m), 1.60–1.72 (2H, m), 2.92–3.02 (1H, m), 3.30–3.38 (1H, m), 6.39 (1H, dd, J 7.6, 1.6); 6.54 (1H, dd, J 7.0, 1.6), 9.56 (1H, dd, J 1, 7.6); δ_C ($CDCl_3$): 13.95, 22.52, 25.47, 31.50, 31.86, 56.18, 61.95, 133.50, 153.15, 192.57; GC–MS (same conditions as those for **4**): t_R 10.57 min (97.2%) [(Z)-isomer at t_R 10.10 min (2.8%)]; MS (70 eV, EI): m/z: 139 (4), 95 (3), 81 (13), 68 (100), 55 (17), 41 (17), 39 (17). HRMS calcd for $C_{10}H_{16}O_2$: 168.1150, found: 168.1146.

4.6. Attempted asymmetric acetylation of (±)-4

IL 1-coated lipase PS (41.8 mg) was added to a solution of (±)-**4** (2.00 g, 13.9 mmol) in (i-Pr)$_2$O (20 mL) and vinyl acetate (1 mL). The mixture was stirred for 4 h at room temperature (18 °C), and filtered through Celite. The filtrate was concentrated in vacuo, and the residue was chromatographed over SiO_2 (20 g). Elution with hexane/EtOAc (100:1–10:1) gave 2.44 g (95%) of ($2R^*$,$3R^*$)-(±)-**6**, ν_{max} (film): 2957 (s), 2932 (s), 2860 (m), 1746 (s), 1458 (m), 1368 (m), 1232 (s), 1036 (m), 890 (m). Since (±)-**6** was of no use, no further characterization was executed.

4.7. Enantiomers of methyl *syn*-2,3-dihydroxyoctanoate 8

4.7.1. (2*R*,3*S*)-(−)-Isomer

AD-mix-α (26.4 g) and $MeSO_2NH_2$ (1.80 g, 18.9 mmol) were added to an ice-cooled and stirred solution of **7** (2.95 g, 18.9 mmol) in t-BuOH (30 mL) and H_2O (30 mL). Stirring was continued overnight at 0–5 °C and then 4 d at room temperature. Next Na_2SO_3 was added to the mixture to quench the reaction. The mixture was then diluted with water, and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over SiO_2 (50 g). Elution with hexane/EtOAc (3:1) gave 3.64 g (98%) of (2R,3S)-(−)-**8** as a colorless oil, n_D^{19} = 1.4482; $[\alpha]_D^{22}$ = −15.9 (c 4.84, $CHCl_3$); ν_{max} (film): 3406 (br m), 2954 (s), 2931 (s), 2860 (m), 1742 (s), 1440 (m), 1273 (m), 1229 (m), 1139 (m), 1095 (m); δ_H ($CDCl_3$): 0.87 (3H, t, J 6.8), 1.25–1.41 (5H, m), 1.47 (1H, m), 1.58–1.68 (2H, m), 2.56 (1H, br), 3.48 (1H, br), 3.82 (3H, s), 3.82–3.90 (1H, m), 4.09–4.18 (1H, m). HRMS calcd for $C_9H_{19}O_4$ [($C_9H_{18}O_4$+H)$^+$]: 191.1283, found: 191. 1294.

4.7.2. (2*S*,3*R*)-(+)-Isomer

Similarly, by employing AD-mix-β, (2S,3R)-(+)-**8** (3.14 g, 88%) was prepared from **7** (2.95 g, 18.9 mmol) as a colorless oil, n_D^{19} = 1.4475; $[\alpha]_D^{22}$ = +17.1 (c 4.41, $CHCl_3$). Its IR and ^1H NMR spectra were identical with those of (2R,3S)-(−)-**8**. HRMS calcd for $C_9H_{19}O_4$ [($C_9H_{18}O_4$+H)$^+$]: 191.1283, found: 191.1290.

4.8. Enantiomers of *trans*-2,3-epoxy-1-octanol 4

4.8.1. (2*R*,3*R*)-(+)-Isomer

Activated (heated at 160 °C under 2 Torr for 3 h) and powdered MS 4 Å (1.8 g) were added to dry CH_2Cl_2 (100 mL) under argon and cooled to −10 °C with a dry ice/CCl_4 bath. To this mixture were added (−)-DET (1.00 g, 4.8 mmol), Ti(Oi-Pr)$_4$ (0.91 g, 3.2 mmol) and t-BuOOH (5.5 M in nonane, 18 mL, 99 mmol) at −10 °C. The mixture was stirred for 10 min at −10 °C. A solution of **3** (8.6 g, 67 mmol) in dry CH_2Cl_2 (10 mL) was added over 15 min to the stirred and cooled mixture at −20 °C. Stirring was continued for 6 h at −20 °C. The mixture was then warmed to 0 °C, and stirred for 5 min at 0 °C. Subsequently, 30% NaOH solution (4.5 mL), dilute $Na_2S_2O_3$ solution (20 mL) and NaCl (3 g) were added, and the mixture was stirred for 10 min. The organic layer was separated, and the aqueous solution was extracted with CH_2Cl_2. The extract was dried ($MgSO_4$), and concentrated in vacuo. The residue was distilled to give (2R,3R)-(+)-**4** (8.25 g, 88%), bp 77–78 °C/2 Torr, which solidified to give colorless crystals, mp 28 °C, $[\alpha]_D^{18}$ = +34.5 (c 5.56, $CHCl_3$). Its IR, ^1H NMR and MS spectra were identical with those of (±)-**4**. GC–MS [same conditions as those used for (±)-**4**]: t_R 7.74 min (89.7%). HRMS calcd for $C_8H_{17}O_2$ [($C_8H_{16}O_2$+H)$^+$]: 145.1227, found: 145.1233.

4.8.2. (2*S*,3*S*)-(−)-Isomer

In the same manner but employing (+)-DET, **3** (8.6 g) gave 7.81 g (81%) of (2S,3S)-(−)-**4**, bp 77–78 °C/2 Torr, which solidified to give colorless crystals, mp 28 °C, $[\alpha]_D^{22}$ = −36.1 (c 4.39, $CHCl_3$). Its IR, ^1H NMR and MS spectra were identical with those of (±)-**4**. GC–MS [same conditions as those used for (±)-**4**]: t_R 7.86 min (94.5%). HRMS calcd for $C_8H_{17}O_2$ [($C_8H_{16}O_2$+H)$^+$]: 145.1227, found: 145.1231.

4.9. Enantiomers of *trans*-2,3-epoxyoctyl 3,5-dinitrobenzoate 9

4.9.1. (2*R*,3*R*)-(+)-Isomer

3,5-Dinitrobenzoyl chloride (11.0 g 47.7 mmol) was added portionwise to a stirred and ice-cooled solution of (2R,3R)-(+)-**4** (6.48 g, 45.0 mmol) and DMAP (50 mg) in dry Et_2O (120 mL) and dry C_5H_5N (15 mL) at 0–5 °C. After the addition, the mixture was left to stand in a refrigerator for 3 d. It was then diluted with ice and water, and extracted with Et_2O. The Et_2O solution was washed successively with $CuSO_4$ solution, water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residual solid (16.5 g) was recrystallized from EtOAc/hexane to give 10.7 g (70%) of crude (2R,3R)-(+)-**9**, mp 48–49 °C, $[\alpha]_D^{20}$ = +33.7 (c 3.38, $CHCl_3$). This was further recrystallized from EtOAc/hexane to give 8.85 g [58% based on (+)-**4**] of (2R,3R)-(+)-**9** as needles, mp 50.5–51.0 °C, $[\alpha]_D^{22}$ = +34.5 (c 3.38, $CHCl_3$); ν_{max} (nujol): 3098 (m), 3086 (w), 1729 (s), 1627 (m), 1543 (s), 1460 (m), 1346 (s), 1173 (m), 886 (m), 731 (m), 721 (m); δ_H ($CDCl_3$): 0.90 (3H, t, J 7.2), 1.30-1.40 (4H, m), 1.40–1.55 (2H, m), 1.58–1.60 (2H, m), 2.94–3.20 (1H, m), 3.14–3.21 (1H, m), 4.27 (1H, dd, J 7, 12), 4.77 (1H, dd, J 3, 12), 9.18–9.20 (2H, m), 9.25–9.26 (1H, m). HRMS calcd for $C_{15}H_{19}N_2O_7$ [($C_{15}H_{18}N_2O_7$+H)$^+$]: 339.1192, found: 339.1165.

4.9.2. (2*S*,3*S*)-(−)-Isomer

In the same manner (2*S*,3*S*)-(−)-**4** (6.48 g) gave 10.41 g (68%) of the first crop, mp 49 °C, $[\alpha]_D^{22}$ = −34.3 (*c* 3.46, $CHCl_3$). This was recrystallized again to give 8.84 g (58%) of (2*S*,3*S*)-(−)-**9** as needles, mp 50 °C, $[\alpha]_D^{23}$ = −34.9 (*c* 3.80, $CHCl_3$). Its IR and ^{1}H NMR spectra were identical with those of (+)-**9**. HRMS calcd for $C_{15}H_{19}N_2O_7$ $[(C_{15}H_{18}N_2O_7+H)^+]$: 339.1192, found: 339.1165.

4.10. Purified enantiomers of *trans*-2,3-epoxy-1-octanol 4 by methanolysis of the corresponding 3,5-dinitrobenzoates 9

4.10.1. (2*R*,3*R*)-(+)-Isomer

At first, K_2CO_3 (700 mg, 5.1 mmol) was added to a stirred and ice-cooled solution of (2*R*,3*R*)-(+)-**9** (8.80 g, 26 mmol) in MeOH (75 mL) and THF (75 mL), and the mixture was stirred for 1 h at 0–5 °C. The solution turned to a dark red color. It was then concentrated in vacuo. The residue was diluted with water, and extracted with Et_2O. The extract was washed successively with water and brine, dried ($MgSO_4$), and concentrated in vacuo to give semi-solid residue. This was triturated with hexane, and filtered to remove crystalline methyl 3,5-dinitrobenzoate, mp 107 °C (4.95 g). The filtrate was concentrated in vacuo. The residue (5.82 g) was chromatographed over SiO_2 (45 g). Elution with hexane/EtOAc (10:1) gave methyl 3,5-dinitrobenzoate (0.81 g). Further elution with hexane/EtOAc (10:1–4:1) gave 5.02 g of (+)-**4**, which was distilled to give pure (2*R*,3*R*)-(+)-**4** (3.57 g, 95%), bp 74–76 °C/2 Torr, which solidified to give prisms, mp 29–30 °C; $[\alpha]_D^{23}$ = +33.4 (*c* 4.59, $CHCl_3$). Its IR, ^{1}H NMR and MS spectra were identical with those of the crude material. GC–MS [same conditions as those for (±)-**4**]: t_R 7.74 min (96.7%). Enantiomeric purity: 96.2% ee (see Section 4.14).

4.10.2. (2*S*,3*S*)-(−)-Isomer

In the same manner (2*S*,3*S*)-(−)-**9** (8.80 g) gave 2.72 g (72%) of (2*S*,3*S*)-(−)-**4**, bp 76–77 °C/2 Torr, which soon solidified to give prisms, mp 31 °C, $[\alpha]_D^{21}$ = −34.5 (*c* 4.50, $CHCl_3$). Its IR, ^{1}H NMR and MS spectra were identical with those of the crude material. GC–MS [same conditions as those for (±)-**4**]: t_R 7.73 min (96.7%). Enantiomeric purity: 95.8% ee (see Section 4.14).

4.11. Enantiomers of *trans*-2,3-epoxyoctanal 5

4.11.1. (2*S*,3*R*)-(−)-Isomer

In the same manner as described in Section 4.4.1 for the preparation of (±)-**5**, (2*R*,3*R*)-(+)-**4** (2.16 g) was oxidized with Dess–Martin periodinane (8.00 g) to give 1.40 g (66%) of (2*S*,3*R*)-(−)-**5** as a colorless oil, n_D^{19} = 1.4350; $[\alpha]_D^{23}$ = −93.4 (*c* 1.21, pentane). Its IR, ^{1}H NMR and MS spectra were identical with those of (±)-**5**. GC–MS (same conditions as those used for **4**): t_R 6.44 min (100%). HRMS calcd for $C_8H_{14}O_2$: 142.0994; found: 142.1014.

4.11.2. (2*R*,3*S*)-(+)-Isomer

In the same manner as described in Section 4.4.1 for the preparation of (±)-**5**, (2*S*,3*S*)-(−)-**4** (2.16 g) was oxidized with Dess–Martin periodinane (8.00 g) to give 1.49 g (70%) of (2*R*,3*S*)-(+)-**5** as a colorless oil, n_D^{16} = 1.4362; $[\alpha]_D^{21}$ = −93.2 (*c* 1.40, pentane). Its IR, ^{1}H NMR and MS spectra were identical with those of (±)-**5**. GC–MS (same conditions as those used for **4**): t_R 6.44 min (99.9%). HRMS calcd for $C_8H_{14}O_2$: 142.0994; found: 142.1007.

4.12. Enantiomers of *trans*-4,5-epoxy-(*E*)-2-decenal 1

4.12.1. (2*E*,4*R*,5*R*)-(+)-Isomer

In the same manner as described in Section 4.5 for the preparation of (±)-**1**, (2*S*,3*R*)-(−)-**5** (1.40 g, 9.8 mmol) and $Ph_3P{=}CHCHO$ (3.65 g, 12 mmol) in dry C_6H_6 (35 mL) gave (2*E*,4*R*,5*R*)-(+)-**1** (1.43 g, 86%) as a colorless oil, n_D^{21} = 1.4760; $[\alpha]_D^{24}$ = +26.2 (*c* 2.24, hexane). Its IR, ^{1}H and ^{13}C NMR, and MS spectra were identical with those of (±)-**1**. GC–MS (same conditions as those used for **4**): t_R 10.61 min (99.7%). HRMS calcd for $C_{10}H_{16}O_2$: 168.1150; found: 168.1163.

4.12.2. (2*E*,4*S*,5*S*)-(−)-Isomer

In the same manner as described in Section 4.5 for the preparation of (±)-**1**, (2*R*,3*S*)-(+)-**5** (1.42 g, 10 mmol) and $Ph_3P{=}CHCHO$ (3.65 g, 12 mmol) in dry C_6H_6 (35 mL) gave (2*E*,4*S*,5*S*)-(−)-**1** (1.45 g, 86%) as a colorless oil, n_D^{19} = 1.4755; $[\alpha]_D^{22}$ = −26.0 (*c* 2.33, hexane). Its IR, ^{1}H and ^{13}C NMR, and MS spectra were identical with those of (±)-**1**. GC–MS (same conditions as those used for **4**): t_R 10.60 min (99.4%). HRMS calcd for $C_{10}H_{16}O_2$: 168.1150; found: 168.1161.

4.13. Determination of the enantiomeric purities of the enantiomers of 3,5-dinitrobenzoate 9 by enantioselective HPLC analysis

Instrument: Shimadzu LC-20AD; Detector: Photo Diode Array SPD-M20A; Column: Chiralpak® AD-H (Daicel, 4.6 mm i.d. × 250 mm); column temperature: 30 °C; eluent: *n*-hexane/EtOH (4:1); flow rate: 1.0 mL/min; detection: 254 nm (UV).

(2*R*,3*R*)-(+)-**9**: t_R 42.5 min; (2*S*,3*S*)-(−)-**9**: t_R 40.7 min. Ee of (2*R*,2*R*)-(+)-**9**: 95.0%: ee of (2*S*,3*S*)-(−)-**9**: 94.6%.

4.14. Determination of the enantiomeric purities of the enantiomers of 4 and 1 by enantioselective GC analysis

4.14.1. GC analysis of the enantiomers of 4

Instrument: Agilent Technologies HP 6890A and HP 5975C; column: heptakis (2,3-di-*O*-acetyl-6-*O*-*t*-butyldimethylsilyl)-β- cyclodextrin (0.25 mm i.d. × 30 m); column temperature: 40–180 °C (+0.7 °C/min), carrier gas, He; flow rate, 0.7 mL/min; detector, TIM. (2*R*,3*R*)-(+)-**4**: t_R 123.9 min; (2*S*,3*R*)-(−)-**4**; t_R 123.1 min. Ee of (2*R*,3*R*)-(+)-**4**: 96.2%; ee of (2*S*,3*S*)-(−)-**4**: 95.8%

4.14.2. GC analysis of the enantiomers of 1

Instrument: same as in Section 4.14.1; Column: Chramix® (0.25 mm i.d. × 30 m); column temperature: 40–180 °C (+0.7 °C/min); carrier gas, He; flow rate, 0.7 mL/min; detector TIM. (2*E*,4*R*,5*R*)-(+)-**1**: t_R 152.3 min; (2*E*,4*S*,5*S*)-(−)-**1**; t_R 149.7 min. Ee of (2*E*,4*R*,5*R*)-(+)-**1**: 97.2%; ee of (2*E*,4*S*,5*S*)-(−)-**1**; 96.2%.

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