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Synthesis and sensory evaluation of all stereoisomers of sedanolide

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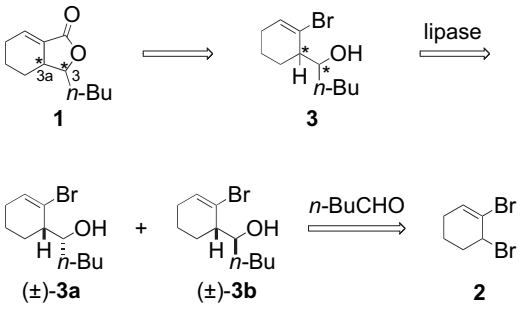
ABSTRACT

Synthesis and sensory evaluation of all stereoisomers of sedanolide (**1**) are described. The asymmetric synthesis was achieved with using the all stereoisomers of bromoalcohol (**3**) prepared by enzymatic resolution and inversion of the secondary alcohol. All four stereoisomers of **1** were obtained in high enantiomeric purities (>99% ee). Their sensory evaluation revealed that there were distinct differences among the stereoisomers.

1. Introduction

Sedanolide (**1**) is the one major constituent of the volatile oil of celery (*Apium graveolens* L., a member of the Umbelliferae family)[1] and has been found to exhibit interesting biological activities, such as inhibition of the growth and toxin production of mycotoxin-producing fungi,[2] chemoprevention of cancer,[3] and mosquito- and nematicidal activities.[4] Uhlig and co-workers isolated some phthalides from celery and concluded that sedanolide (**1**) contributes greatly to the perception of celery flavor.[5] Although Kurobayashi and co-workers reported that it existed as a single stereoisomer in fresh celery,[6] a sensory comparison among all stereoisomers has not been reported yet. The synthesis of racemate was achieved by several groups[7] and Yamashita and co-workers synthesized (3*S*,3a*R*)-**1**, (3*R*,3a*S*)-**1**, and (3*S*,3a*S*)-**1** using intramolecular Diels–Alder reaction.[8] In this study, we developed concise synthesis of all stereoisomers of sedanolide (**1**) and evaluated their odors.

Our synthetic plan is shown in Scheme 1. We thought that the synthesis of all stereoisomers of sedanolide (**1**) would be achieved by carboxylation and lactonization of chiral bromoalcohols (**3**), which could be obtained by enzymatic resolution of racemate. Racemic bromoalcohols [(±)-**3a** and (±)-**3b**] would be obtained from a known dibromide (**2**)[9] by Barbier reaction with valeraldehyde.



Scheme 1. Retrosynthetic analysis.

2. Results and discussion

2.1. Synthesis of the racemate

As shown in Scheme 2, 2,3-dibromocyclohexene (**2**)[9] was reacted with valeraldehyde in the presence of zinc powder in aqueous medium to give a separable diastereomeric mixture of **3a** and **3b** (78:22). Their relative stereochemistry was determined by transforming them into sedanolides [(±)-**1a** and (±)-**1b**] and comparing their NMR data with those reported.[7] Each isomer [(±)-**3a** and (±)-**3b**] was lithiated with *tert*-butyllithium and the genarated dianion was treated with CO_2 gas to give the hydroxy acid, which was converted into racemic sedanolide [(±)-**1a** and (±)-**1b**] by the acidic lactonization, respectively.

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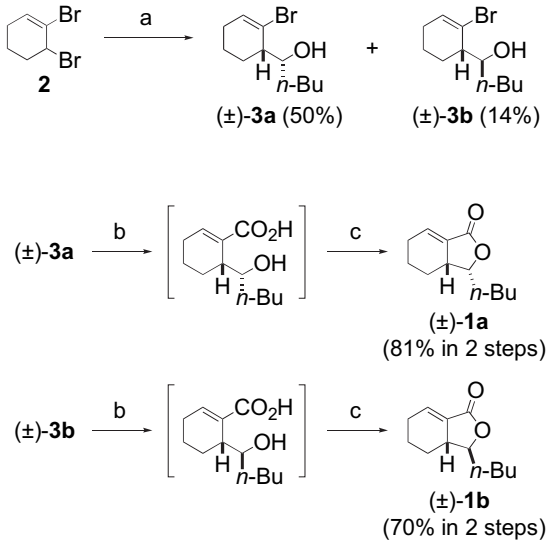
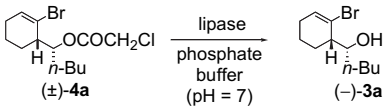


Scheme 2. Reagents and conditions: (a) *n*-BuCHO, Zn powder, NH_4Cl aqueous, THF; (b) *t*-BuLi, Et_2O; CO_2 (gas); H^+; (c) TsOH, PhMe.

2.2. Preliminary experiments for asymmetric synthesis

Next we tried an enzymatic resolution of the bromoalcohol (**3**) for asymmetric synthesis. Both the enzymatic acylation of either (±)-**3a** or (±)-**3b** by using vinyl acetate or isopropenyl acetate and the enzymatic hydrolysis of acetate were failed. However, chloroacetate [(±)-**4a**] was hydrolyzed smoothly by lipase from *Candida*. The only lipase from *Candida* could promote this reaction in spite of the ineffectiveness of other lipases from *Pseudomonas*, porcine pancreas, and *Penicillium*. As shown in Table 1, lipase OF (Meito) was the most effective for optical resolution of (±)-**4a** among the lipases from *Candida*. Racemic **4a** was treated with lipase OF at room temperature for 12 h to give (−)-**3a**, whose enantiomeric purity was estimated to be 96% ee by GLC analysis.[10] The absolute configuration of (−)-**3a** was determined by transforming into sedanolide [(3*R*,3a*R*)-(+)-**1**] and comparing its NMR data and $[\alpha]_D$ value with those reported for its enantiomer.[8] Unfortunately this lipase was not useful for another isomer [(±)-**3b**], and we therefore tried inversion of the secondary alcohol. Although the Mitsunobu reaction failed, reduction of ketone [(±)-**5**, obtained by PCC oxidation of (±)-**3a**] with tri(*sec*-butyl)borohydride (L-Selectride®) was followed by treatment with alkaline hydrogen peroxide to give (±)-**3b** in excellent stereoselectivity (Scheme 3). These results suggested that we could obtain all stereoisomers of **3** by enzymatic resolution and inversion of the secondary alcohol.

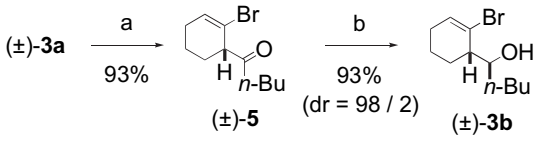
Table 1
Enzymatic resolution of (±)-**4a** by lipase from *Candida*



Lipase	Time	Conversion	ee of (−)-**3a**	*E* value
CRL (Sigma)	21 h	58%	56%	8
CAL (Novo)	5 d	n.r.	_	_
AY (Amano)	12 h	29%	89%	25
MY (Meito)	12 h	43%	77%	13
OF (Meito)	12 h	32%	96%	77

2.3. Achivement of asymmetric synthesis

Esterification of (±)-**3a** with chloroacetyl chloride gave chloroacetate [(±)-**4a**] in high yield. Enzymatic hydrolysis of (±)-**4a** with lipase OF gave alcohol [(−)-**3a**] and recovered substrate [(−)-**4a**] in 46% (94.2% ee) and 52% (82.0% ee) yield, respectively. The alcohol [(−)-**3a**, 94.2% ee] was acylated and hydrolyzed with lipase again to give the enantiomerically enriched alcohol [(−)-**3a**] with 99.8% ee. On the other hand, the recovered substrate [(−)-**4a**] was treated with lipase again and then methanolysis of recovered substrate gave the enantiomer [(+)-**3a**] with 99.8% ee. Both enantiomers were converted into ketones by PCC oxidation and then reduced with L-Selectride® to give (−)-**3b** (99.5% ee) and (+)-**3b** (99.5% ee), respectively.



Scheme 3. Reagents and conditions: (a) PCC, Celite®, CH_2Cl_2; (b) L-Selectride®, THF; NaOH, H_2O_2, H_2O.

With four stereoisomers of bromoalcohol **3** in hand, we achieved the synthesis of all stereoisomers of **1** under the same conditions mentioned above, namely, lithiation, carboxylation, and lactonization (Scheme 4). Synthetic enantiomers were completely identical with racemic sedanolides in their IR and NMR spectral properties, and their enantiomeric purities were shown to be 99.9–99.1% ee by GLC analysis.[10] The absolute configurations of them were confirmed by comparing their NMR data and specific rotations with those reported.[8]

2.4. Sensory evaluation

The odors of the four stereoisomers were evaluated by special panelists and the odor thresholds were measured by a triangle test.[11] The results of the sensory evaluations are shown in Table 2. There are remarkable differences among their odors and odor thresholds. Although (3*S*,3a*R*)-**1**, the major isomer in fresh celery, had the most characteristic odor of natural celery leaf, the enantiomer [(3*R*,3a*S*)-**1**] had spicy aroma like celery seeds. About diastereomer, (3*R*,3a*R*)-**1** had strong aroma like celery stem and (3*S*,3a*S*)-**1** lacked celery odor. It was very interesting result that the odor characters among isomers were obviously different, such as leaf-like, seed-like, and stem-like as well as the strength of odor. (3*S*,3a*R*)-isomer of **1** had the strongest odor, which was about 20 times stronger than the antipode and about 100 times stronger than the other two diastereomers.

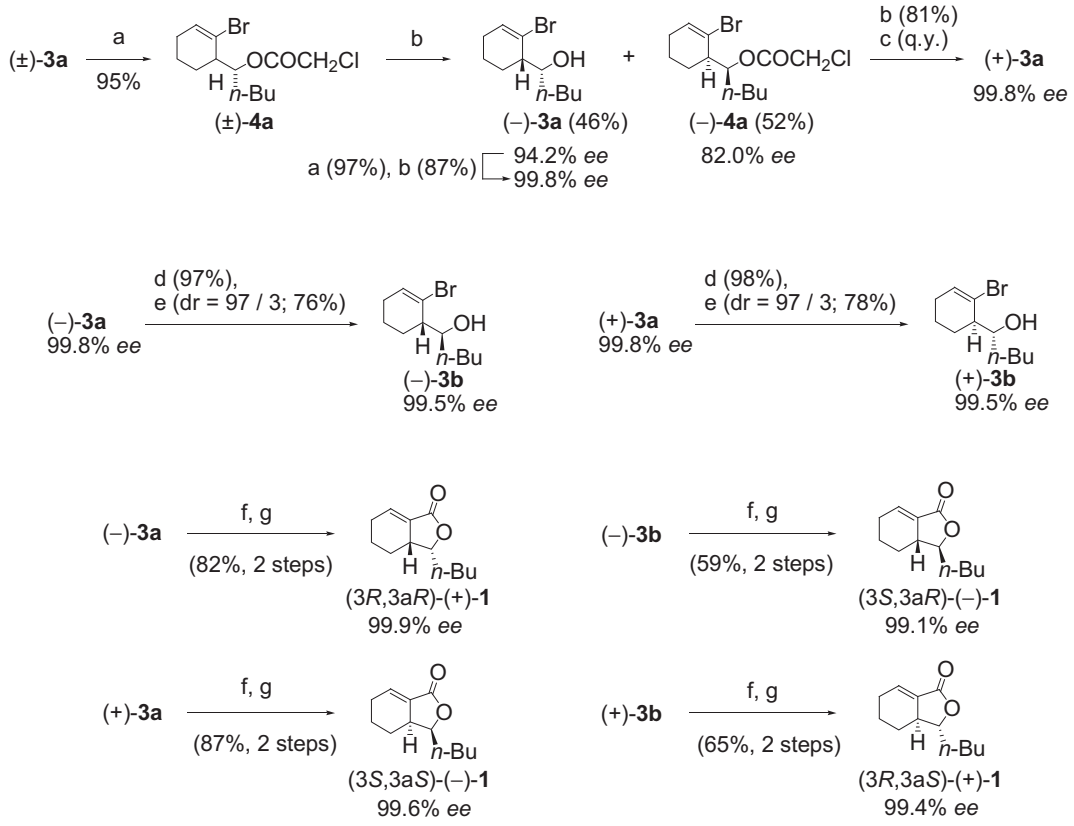
3. Conclusion

We achieved the synthesis of all stereoisomers of sedanolide, starting from 2,3-dibromocyclohexene (**2**) in 10–23% overall yields through 7–9 steps. In the sensory evaluation of these enantiomers, we found obvious differences among their aroma characters and odor thresholds and (3*S*,3a*R*)-**1** had the most characteristic odor of natural celery leaf.

4. Experimental

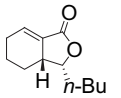
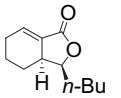
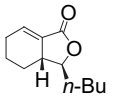
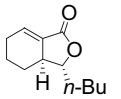
4.1. General

All air- and/or water-sensitive reactions were carried out under argon atmosphere in dry solvents. All solvents were reagent grade. Tetrahydrofuran and diethyl ether were freshly distilled from sodium/benzophenone under argon. Dichloromethane was freshly distilled from P_2O_5 under argon. Toluene and methanol were dried over 4 Å-molecular sieves and 3 Å-molecular sieves, respectively. *n*-Hexane and ethyl acetate were used without further purification. All melting points (mps) were uncorrected.



Scheme 4. Reagents and conditions: (a) $ClCH_2COCl$, Et_2O, pyr., DMAP; (b) lipase OF, phosphate buffer (pH=7); (c) K_2CO_3, MeOH; (d) PCC, Celite®, CH_2Cl_2; (e) L-Selectride®, THF; NaOH, H_2O_2, H_2O; (f) *t*-BuLi, Et_2O; CO_2 (gas); H^+; (g) TsOH, PhMe.

Table 2
Sensory evaluation of chiral sedanolides

Structure	Odor description[a]	Odor threshold[b] (ppm)
 (3*R*,3a*R*)-(+)-**1**	Natural celery stem odor, herbal, and bitter.	1.6
 (3*S*,3a*S*)-(–)-**1**	Very weak odor. No impression of celery.	1.9
 (3*S*,3a*R*)-(–)-**1**	Natural celery leaf odor, herbal, and strong bitter.	1.3×10^{-2}
 (3*R*,3a*S*)-(+)-**1**	Celery seed odor, heavy, and spicy. Weak impression of celery.	2.7×10^{-1}

[a] Evaluated as 50 ppm solution in water.
[b] Calcuated on the result of a triangle test by 26 trained panelists.

Melting points were recorded on a Yanaco Micro Melting Point Apparatus. Infrared spectra (IR) were measured on a Jasco FT/IR-470 plus spectrometer. Proton magnetic resonance spectra (^{1}H NMR) and carbon magnetic resonance spectra (^{13}C NMR) were recorded on a JEOL JNM-ECX 400 spectrometer (^{1}H NMR 400 MHz, ^{13}C NMR 100 MHz). Chemical shifts are reported in parts per million (δ) relative to internal chloroform (^{1}H: C*H*Cl$_3$ at δ 7.26; ^{13}C: *C*DCl$_3$ at δ 77.0). Optical rotations were measured on a Jasco P-1030 polarimeter. HRMS were recorded with a JEOL JMS-700T (FAB) or a JEOL JMS-T100LC AccuTOF (ESI). GC–MS analyses were carried out with an Agilent 6890N gas chromatograph (TC-1701 capillary column 30 m, ID 0.25 mm, film 0.25 μm) equipped with an Agilent 5973 Mass Selective Detector. The enantiomeric excess was determined by gas chromatography using a chiral separative column, CHIRAMIX® (30 m, ID 0.25 mm, film 0.25 μm).[10] The carrier gas was nitrogen with a flow rate of 0.7 mL/min. Injector and detector temperatures were 250 and 230 °C, respectively. The oven temperature was 40–180 °C, raised at 0.7 °C/min. Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm Merck silica gel 60 F_{254} precoated glass-backed plates. Compounds were visualized by ultraviolet light (254 nm), iodine vapor or phosphomolybdic acid spray reagent. Column chromatography was performed on Merck silica gel 60 or Kanto Chemical silica gel 60N (neutral).

4.1.1. (1R,1′S*)-1-(2′-Bromocyclohex-2′-enyl)pentan-1-ol [(±)-**3a**] and (1S*,1′S*)-1-(2′-bromocyclohexa-2′-enyl)pentan-1-ol [(±)-**3b**].* To a suspension of zinc powder (2.35 g, 36.0 mmol), saturated aqueous ammonium chloride solution (36 mL) and tetrahydrofuran (12 mL) at −5 °C was added *n*-valeraldehyde (3.10 g, 36.0 mmol) over 5 min. Then to the mixture at −5 °C was dropped a solution of 2,3-dibromo-1-cyclohexene (**2**, 5.75 g, 24.0 mmol) in tetrahydrofuran (60 mL) over 2 h. After being stirred at the same temperature for 1 h, water and ether were added to the mixture, and the mixture was filtered through Celite® pad to remove the insoluble material. The aqueous layer separated from the filtrate was extracted with ether. The

combined organic layer was washed with aqueous sodium bisulfate solution, aqueous sodium carbonate solution and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was chromatographed on silica gel (200 g). Elution with *n*-hexane/ethyl acetate (30/1–10/1) gave (±)-**3a** (2.94 g, 50%) and (±)-**3b** (0.84 g, 14%) both as colorless oils. Compound (±)-**3a**: IR (film) 3464, 2932, 2859, 1640, 1456, 1329, 1066, 975, 887, 709 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.92 (t, J=7.1 Hz, 3H), 1.26–1.60 (m, 8H), 1.70–1.85 (m, 3H), 2.04–2.08 (m, 2H), 2.38 (m, 1H), 4.20 (m, 1H), 6.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.05, 20.77, 22.74, 23.29, 27.78, 28.63, 33.22, 47.14, 71.74, 126.15, 133.96; GC–MS: 246 ($[M-1]^+$), 160 (30), 87 (13), 81 (100), 69 (70), 57 (13), 51 (4), 41 (30), 29 (8); HRMS (FAB) calcd for $C_{11}H_{20}BrO$ $(M+H)^+$: 247.0698, found 247.0722. Compound (±)-**3b**: IR (film) 3357, 2859, 1638, 1450, 1325, 1072, 1019, 970, 718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.91 (t, J=7.1 Hz, 3H), 1.28–1.59 (m, 8H), 1.67–1.75 (m, 2H), 1.87 (m, 1H), 2.03–2.08 (m, 2H), 2.65 (m, 1H), 4.11 (br, 1H), 6.18 (dt, J=1.8, 4.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.09, 20.21, 22.63, 24.71, 27.84, 28.82, 31.83, 47.67, 73.93, 124.33, 132.27; GC–MS: 246 ($[M-1]^+$), 160 (28), 87 (15), 81 (100), 69 (76), 57 (14), 51 (5), 41 (31), 29 (7); HRMS (FAB) calcd for $C_{11}H_{20}BrO$ $(M+H)^+$: 247.0698, found 247.0679.

4.1.2. (3R,3aR*)-Sedanolide [(±)-**1a**].* To a solution of bromoalcohol [(±)-**3a**, 247 mg, 1.0 mmol] in ether (13 mL) was added a pentane solution of *tert*-butyllithium (1.48 M, 3.4 mL, 5.0 mmol) at −78 °C over 15 min. After being stirred at the same temperature for 5 min, CO_2 gas was bubbled into the reaction mixture at the same temperature for 0.5 h. Then to the mixture at −78 °C was dropped methanol (0.5 mL) and the mixture was allowed to warm to room temperature. The reaction mixture was diluted with *n*-hexane and extracted with aqueous sodium carbonate solution. The combined aqueous layer was washed with *n*-hexane and acidified by the addition of 3 N HCl at 0 °C. To the acidic solution was saturated with NaCl and the resulting mixture was extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate and concentrated in vacuo to give a crude hydroxy acid (286 mg). After a solution of crude hydroxy acid (286 mg) and catalytic amount of TsOH in toluene (13 mL) was stirred at room temperature for 12 h, the reaction mixture was washed with saturated aqueous sodium bicarbonate solution and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was chromatographed on silica gel (7 g). Elution with *n*-hexane/ethyl acetate (30/1–10/1) gave (±)-**1a** (157 mg, 81%) as a colorless oil. For analysis further distillation with using Kugelrohr gave (±)-**1a** as a colorless oil. IR (film): 2936, 2865, 1758, 1683, 1454, 1332, 1225, 1185, 1028, 943, 752, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, J=7.1Hz, 3H), 1.24–1.60 (m, 8H), 1.87–1.97 (m, 2H), 2.14–2.38 (m, 2H), 3.00–3.10 (m, 1H), 4.63 (dt, J=2.8, 9.2 Hz, 1H), 6.82 (dd, J=7.1, 3.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.90, 21.14, 22.45, 22.54, 25.12, 27.51, 31.49, 39.69, 81.84, 129.57, 136.18, 170.18; GC–MS: 194 (1, $[M-1]^+$), 137 (8), 108 (100), 91 (4), 79 (36), 53 (5), 41 (6), 29 (4); HRMS (ESI) calcd for $C_{12}H_{18}NaO_2$ $(M+Na)^+$: 217.1205, found 217.1222.

4.1.3. (3S,3aR*)-Sedanolide [(±)-**1b**].* In the same manner described for the synthesis of (±)-**1a**, (±)-**3b** (247 mg, 1.0 mmol) afforded sedanolide (±)-**1b** (136 mg, 70%) as a colorless oil. For analysis further distillation with using Kugelrohr gave (±)-**1b** as colorless crystals. Mp 34.5–35.0°C; IR (film): 2933, 2861, 1763, 1683, 1455, 1422, 1327, 1249, 1226, 1183, 1025, 930, 726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.91 (t, J=7.3 Hz, 3H), 1.16 (m, 1H), 1.30–1.60 (m, 5H), 1.70–1.82 (m, 2H), 1.94 (m, 1H), 2.06 (m, 1H), 2.19 (m, 1H), 2.35 (m, 1H), 2.49 (m, 1H), 3.96 (ddd, J=8.9, 7.3, 5.3 Hz, 1H), 6.77 (dd, J=6.9, 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.88, 20.75, 22.51, 24.98, 25.36, 27.51, 34.31, 43.06, 85.32, 131.14, 135.18, 170.23; GC–MS: 194 (1, $[M-1]^+$), 137 (8), 108 (100), 91 (4), 79 (36), 53 (5), 41 (6), 29 (4); HRMS (ESI) calcd for $C_{12}H_{18}NaO_2$ $(M+Na)^+$: 217.1205, found 217.1222.

4.1.4. (1R,1′S*)-1-(2′-Bromocyclohex-2′-enyl)pentyl 2-chloroacetate [(±)-**4a**].* To a stirred solution of (±)-**3a** (10.0 g, 40.5 mmol), pyridine (5.8 g, 73.0 mmol) and DMAP (0.1 g, 0.8 mmol) in ether (100 mL) was added chloroacetyl chloride (6.9 g, 60.8 mmol) at 2–8 °C over 20 min. After stirred at room temperature for 1 h, to the mixture was added water (100 mL) at 0 °C and stirred for several min. The aqueous layer, which was separated from the mixture was extracted with ether. The combined organic layer was washed with aqueous copper sulfate solution, water, aqueous sodium bicarbonate solution and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was chromatographed on silica gel (300 g). Elution with *n*-hexane/ethyl acetate (60/1–40/1) gave (±)-**4a** (12.3 g, 94%) as a colorless oil. IR (film): 2955, 2870, 1738, 1643, 1456, 1411, 1286, 1183, 973, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.90 (t, J=6.9 Hz, 3H), 1.20–1.40 (m, 4H), 1.50–1.65 (m, 2H), 1.70–1.90 (m, 4H), 2.05 (m, 2H), 2.53 (m, 1H), 4.02 (s, 2H), 5.48 (dt, J=2.5, 7.1 Hz, 1H), 6.21 (dt, J=4.1, 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.90, 19.95, 22.49, 24.30, 27.44, 27.76, 31.14, 40.97, 44.75, 76.32, 123.71, 133.07, 166.50; HRMS (ESI) calcd for $C_{13}H_{20}BrClNaO_2$ $(M+Na)^+$: 345.0233, found 345.0225.

*4.1.5. (1R,1′S)-1-(2′-Bromocyclohex-2′-enyl)pentan-1-ol [(−)-**3a**] and (1S,1′R)-1- (2′-bromocyclohex-2′-enyl)pentan-1-ol [(+)-**3a**].* A mixture of (±)-**4a** (10.0 g, 30.9 mmol), Lipase OF (3.0 g) and a 0.1 M phosphate buffer solution (pH 7.0, 200 mL) was stirred at room temperature for 25 h. After filtration through Celite®, filtrate was extracted with ether and the extract was washed with aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was chromatographed on silica gel (300 g). Elution with *n*-hexane/ethyl acetate (60/1–15/1) gave alcohol (−)-**3a** (5.88 g, 46%) as a product and chloroacetate (−)-**4a** (3.07 g, 52%) as a residual substrate. In the same manner described for the synthesis of (±)-**4a**, alcohol (−)-**3a** (3.35 g, 13.6 mmol) afforded chloroacetate (+)-**4a** (4.3 g, 97%) as a colorless oil. $[\alpha]_D^{20}$ +38.6 (*c*1.60, $CHCl_3$); HRMS (ESI) calcd for $C_{13}H_{20}BrClNaO_2$ $(M+Na)^+$: 345.0233, found 345.0233. The chloroacetate (+)-**4a** (4.17 g, 12.9 mmol) was similarly hydrolyzed with Lipase OF under the condition mentioned above excluding the reaction time (24 h) to give alcohol (−)-**3a** (2.8 g, 87%, 99.8% ee) as a colorless oil. $[\alpha]_D^{20}$ −23.9 (*c*1.25, $CHCl_3$); HRMS (FAB) calcd for $C_{11}H_{20}BrO$ $(M+H)^+$: 247.0698, found 247.0739. On the other hand chloroacetate (−)-**4a** (5.04 g, 15.6 mmol), which was obtained as a residual substrate on the first enzymatic hydrolysis, was hydrolyzed again with Lipase OF similarly under the condition mentioned above excluding the reaction time (60 h) to give residual chloroacetate (−)-**4a** (2.8 g, 81%) as a colorless oil. $[\alpha]_D^{20}$ −40.8 (*c* 1.19, $CHCl_3$); HRMS (ESI) calcd for $C_{13}H_{20}BrClNaO_2$ $(M+Na)^+$: 345.0233, found 345.0216. A mixture of (−)-**4a** (2.59 g, 8.0 mmol) and potassium carbonate (0.13 g, 0.9 mmol), and MeOH (75 mL) was stirred at room temperature for 3 h. After being neutralized with acetic acid, the reaction mixture was concentrated in vacuo. The residue was chromatographed on silica gel (80 g). Elution with *n*-hexane/ethyl acetate (60/1–15/1) gave alcohol (+)-**3a** (1.96 g, 99%, 99.8% ee) as a colorless oil. $[\alpha]_D^{20}$ +24.6 (*c* 1.04, $CHCl_3$); HRMS (FAB) calcd for $C_{11}H_{20}BrO$ $(M+H)^+$: 247.0698, found 247.0679.

*4.1.6. (S)-1-(2′-Bromocyclohex-2′-enyl)pentan-1-one [(+)-**5**].* To a stirred mixture of pyridinium chlorochromate (2.16 g, 10.0 mmol), Celite® (3.24 g), and dichloromethane (80 mL) was added alcohol (−)-**3a** (1.24 g, 5.0 mmol) at room temperature for 5 min. After being stirred at room temperature for overnight, the mixture was decantated and filtered through silica gel pad and eluted with ether

and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel (25 g). Elution with *n*-hexane/ethyl acetate (100/1–50/1) gave ketone (+)-**5** (1.19 g, 97%, 99.6% ee) as a colorless oil. $[\alpha]_D^{20}$ +110 (*c* 1.30, $CHCl_3$); IR (film): 2933, 2871, 1715, 1645, 1448, 1334, 1125, 1081, 1051, 979 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.91 (t, *J*=7.3 Hz, 3H), 1.28–1.37 (m, 2H), 1.55–1.72 (m, 4H), 1.84 (m, 1H), 1.94 (m, 1H), 2.05–2.20 (m, 2H), 2.46–2.67 (m, 2H), 3.50 (m, 1H), 6.28 (dt, *J*=1.4, 4.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.87, 18.53, 22.29, 25.76, 27.28, 27.62, 41.14, 56.10, 118.60, 132.58, 209.96; HRMS (ESI) calcd for $C_{11}H_{17}BrNaO$ $(M+Na)^+$: 267.0361, found 267.0369.

*4.1.7. (R)-1-(2′-Bromocyclohex-2′-enyl)pentan-1-one [(−)-**5**].* In the same manner described for the synthesis of (+)-**5**, (+)-**3a** (1.24 g, 5.0 mmol) afforded ketone (−)-**5** (1.19 g, 98%, 99.4% ee) as a colorless oil. $[\alpha]_D^{20}$ −108 (*c* 1.01, $CHCl_3$); HRMS (ESI) calcd for $C_{11}H_{17}BrNaO$ $(M+Na)^+$: 267.0361, found 267.0380.

*4.1.8. (1S,1′S)-1-(2′-Bromocyclohex-2′-enyl)pentan-1-ol [(−)-**3b**].* To a stirred solution of ketone (+)-**5** (490 mg, 2.0 mmol) and tetrahydrofuran (24 mL) was added a tetrahydrofuran solution of L-Selectride® (1.0 M, 3.0 mL, 3.0 mmol) at −78 °C over 10 min. After being stirred at −78 °C for 1 h and at 0°C for 1 h, 3 N NaOH solution (10 mL) and 35% H_2O_2 solution (10 mL) were added successively at 0 °C for 25 min and the mixture was allowed to warm to room temperature over 0.5 h, and heated at 60 °C for 1 h. After being cooled to room temperature, the aqueous layer, which was separated from the mixture was extracted with ether. The combined organic layer was washed with brine, aqueous sodium thiosulfate solution and brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was chromatographed on silica gel (25 g). Elution with *n*-hexane/ethyl acetate (50/1–30/1) gave (−)-**3b** (374 mg, 76%, 99.5% ee) as a colorless oil. $[\alpha]_D^{20}$ −25.3 (*c*1.02, $CHCl_3$); HRMS (FAB) calcd for $C_{11}H_{20}BrO$ $(M+H)^+$: 247.0698, found 247.0679.

*4.1.9. (1R,1′R)-1-(2′-Bromocyclohex-2′-enyl)pentan-1-ol [(+)-**3b**].* In the same manner described for the synthesis of (−)-**3b**, (−)-**5** (490 mg, 2.0 mmol) afforded alcohol (+)-**3b** (384 mg, 78%, 99.4% ee) as a colorless oil. $[\alpha]_D^{20}$ +23.7 (*c* 1.17, $CHCl_3$); HRMS (FAB) calcd for $C_{11}H_{20}BrO$ $(M+H)^+$: 247.0698, found 247.0709.

*4.1.10. (3R,3aR)-(+)-Sedanolide (**1**).* In the same manner described for the synthesis of (±)-**1a**, (−)-**3a** (0.247 g, 1.0 mmol) afforded (3*R*,3a*R*)-(+)-sedanolide (**1**) (0.159 g, 82%, 99.9% ee) as a colorless oil. For the sensory evaluation further distillation with using Kugelrohr gave (3*R*,3a*R*)-(+)-sedanolide (**1**) as a colorless oil. $[\alpha]_D^{20}$ +92.8 (*c* 1.05, $CHCl_3$); HRMS (ESI) calcd for $C_{12}H_{18}NaO_2$ $(M+Na)^+$: 217.1205, found 217.1222.

*4.1.11. (3S,3aS)-(−)-Sedanolide (**1**).* In the same manner described for the synthesis of (±)-**1a**, (+)-**3a** (0.247 g, 1.0 mmol) afforded (3*S*,3a*S*)-(−)-sedanolide (**1**) (0.168 g, 87%, 99.6% ee) as a colorless oil. For the sensory evaluation further distillation with using Kugelrohr gave (3*S*,3a*S*)-(−)-sedanolide (**1**) as a colorless oil. $[\alpha]_D^{20}$ −91.3 (*c* 1.10, $CHCl_3$); HRMS (ESI) calcd for $C_{12}H_{18}NaO_2$ $(M+Na)^+$: 217.1205, found 217.1222.

*4.1.12. (3S,3aR)-(−)-Sedanolide (**1**).* In the same manner described for the synthesis of (±)-**1a**, (−)-**3b** (0.281 g, 1.13 mmol) afforded (3*S*,3a*R*)-(−)-sedanolide (**1**) (0.130 g, 59%, 99.1% ee) as a colorless oil. For the sensory evaluation further distillation with using Kugelrohr gave (3*S*,3a*R*)-(−)-sedanolide (**1**) as colorless crystals. Mp 33.5–34.5 °C; $[\alpha]_D^{20}$ −71.3 (*c* 1.15, $CHCl_3$); HRMS (ESI) calcd for $C_{12}H_{18}NaO_2$ $(M+Na)^+$: 217.1205, found 217.1222.

*4.1.13. (3R,3aS)-(+)-Sedanolide (**1**).* In the same manner described for the synthesis of (±)-**1a**, (+)-**3b** (0.288 g, 1.16 mmol) afforded (3*R*,3a*S*)-(+)-sedanolide (**1**) (0.147 g, 65%, 99.4% ee) as a colorless oil. For the sensory evaluation further distillation with using Kugelrohr gave (3*R*,3a*S*)-(+)-sedanolide (**1**) as colorless crystals. Mp 33.5–34.5 °C; $[\alpha]_D^{20}$ +71.8 (*c* 1.06, $CHCl_3$); HRMS (ESI) calcd for $C_{12}H_{18}NaO_2$ $(M+Na)^+$: 217.1205, found 217.1222.

4.2. Sensory evaluation

Each synthetic samples were diluted with water to 50 ppm and the odor description was given in the evaluation of its headspace by special panelists.

A defined amount of each synthetic compound, dissolved in ethanol (1%), was diluted with water to the several concentrations step by step. The initial concentrations, dependent on the substances, were determined in preliminary experiments.

Odor detection thresholds were determined by the triangle test[11] using aqueous ethanol as a blank. The samples were presented to 26 special panelists in order of decreasing concentration, and the threshold values were calculated as the average.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.11.035.

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