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Asymmetric Synthesis and Sensory Evaluation of Sedanenolide

Daichi OGURO[1,2] and Hidenori WATANABE[2,†]

[1]*Technical Research Institute, R&D Center, T. Hasegawa Co., Ltd., 29-7 Kariyado, Nakahara-ku, Kawasaki, Kanagawa 211-0022, Japan*
[2]*Department of Applied Biological Chemistry, Graduate School of Agricultural and Life Sciences, The University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113-8657, Japan*

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The synthesis and sensory evaluation of enantiomeric sets of sedanenolide (1) and 3-butylphthalide (3) are described. The asymmetric synthesis was achieved *via* the intramolecular Diels-Alder reaction of chiral propargylester (5) which was prepared from optically active propargyl alcohol (4) and 2,4-pentadienoic acid. The sensory evaluation of these enantiomers revealed that there were distinct differences between their aroma character and odor threshold.

Key words: sedanenolide; 3-butylphthalide; celery; sensory evaluation

Sedanenolide (**1**), also called senkyunolide, was independently isolated in 1977 from the essential oil of celery (*Apium graveolens* L.)[1] and senkyu (*Cnidium officinale* Makino)[2] by two groups. It was found to have such interesting biological activities as skin-whitening,[3] inhibiting the proliferation in primary cultures of mouse aorta smooth muscle cells,[4] and mosquitocidal, antimicrobial and nematicidal activities.[5] Phthalides widely exists in plants of the Umbelliferae family (Fig. 1), and it has been reported that sedanenolide (**1**), sedanolide (**2**) and 3-butylphthalide (**3**) substantially contributed to the perception of celery flavor.[6] Kurobayashi *et al.* have reported that **1** influenced the taste of chicken broth most among compounds **1**–**3** and that its (*S*)-(−)-enantiomer (96% *ee* in natural celery) was more strongly reminiscent of natural celery than its antipode.[7–9]

We have previously synthesized all stereoisomers of **2** and elucidated the difference in odor among them.[10] Kosaka *et al.* have achieved the asymmetric synthesis of **3**,[11] and Bartschat *et al.* have accomplished the sensory evaluation of both the enantiomers of **3**.[12] However, only the synthesis of racemic **1** has been reported, and the enantiomers have not been synthesized before.[13] We now report the synthesis of both the enantiomers of **1** and **3** which will hopefully enable us to evaluate in detail the difference in aroma between the enantiomers.

Our synthetic plan is shown in Scheme 1. We anticipated synthesizing both enantiomers of **1** by the intramolecular Diels-Alder reaction of **5**, which could be obtained from known chiral alcohol **4** and 2,4-pentadienoic acid, with subsequent isomerization of the double bond. Each enantiomer of **1** would be readily converted into optically active **3** by oxidation.[2] Suzuki *et al.* and Tanaka *et al.* have reported a similar approach for the synthesis of **2** by using an allylic alcohol instead of **4**.[14,15]

Results and Discussion

The key Dieles-Alder reaction was investigated first by using a racemate (Scheme 2). Esterification of propargyl alcohol (±)-**4**[16] with 2,4-pentadienoic acid gave cyclization precursor (±)-**5**. A solution of (±)-**5** in toluene was heated in an autoclave at 220 °C in the presence of an antioxidant to directly give (±)-**1** and a small amount of (±)-**3** *via* the desired Dieles-Alder reaction and subsequent isomerization of the double bond. Separation by silica gel column chromatography gave (±)-**1** and (±)-**3** in respective 50% and 13% yields, whose NMR spectral data were in accordance with those reported.[17]

We next applied this method to the asymmetric synthesis of **1** and **3**. The enzymatic resolution of (±)-**4** respectively gave known (*S*)-(−)-**4** and (*R*)-(+)-**4** in 99.9% *ee* and 97.4% *ee* by using the modified method reported by Abad *et al.*[18] (Scheme 3). Each compound was reacted with 2,4-pentadienoic acid and heated to give chiral **1** together with a small amount of chiral **3**. These synthetic enantiomers were identical with the racemate in their IR and NMR spectral properties, and their optical purity was found to be 99.6–96.2% *ee* by a GLC analysis.[19] A small decrease in optical purity indicates partial racemization of the substrate and/or the product under the reaction conditions (Scheme 4).

We evaluated the odors of the enantiomers of both **1** and **3** as shown in Table 1. Both *S*-forms, the major isomers in natural celery, had the fresh and strong aroma of the celery stem, but their antipodes lacked this fresh celery aroma. The *S*-forms also had a 4–5 times stronger odor than their antipodes. Bartschat *et al.* have reported the difference in sensory characteristics and odor thresholds between the enantiomers of **3** by enantioselective gas chromatography/olfactometry.[12] In addition to their reported results, our present results reveal that the *S*-form of **1**, as well as of **3**, was superior as a flavor component to the *R*-form.

Conclusion

We achieved an asymmetric synthesis of sedanenolide (**1**) and also obtained enantiomers of 3-butylphthalide

† To whom correspondence should be addressed. Tel: +81-3-5841-5119; Fax: +81-3-5841-8019; E-mail: ashuten@mail.ecc.u-tokyo.ac.jp

(**3**) as by-products, starting from racemic 1-heptyn-3-ol [(±)-**4**] in a 3–12% overall yield through four steps. A sensory evaluation of these enantiomers indicated obvious differences among their aroma characters and odor thresholds. Both *S*-enantiomers of **1** and **3** were found to be superior in odor to their antipodes.

Experimental

Instrumentation and reagents. All air- and/or water-sensitive reactions were carried out in an argon atmosphere with dry solvents, all solvents being of reagent grade. Tetrahydrofuran (THF) and diethyl ether were freshly distilled from sodium/benzophenone under argon. Toluene and methanol were respectively dried over 4-Å and 3-Å molecular sieves. *n*-Hexane and ethyl acetate were used without further purification. Infrared spectra (IR) were measured by a Jasco FT/IR-470 Plus spectrometer. Proton magnetic resonance spectra (^{1}H-NMR) and carbon magnetic resonance spectra (^{13}C-NMR) were recorded by a Jeol JNM-ECX 400 spectrometer (^{1}H-NMR at 400 MHz

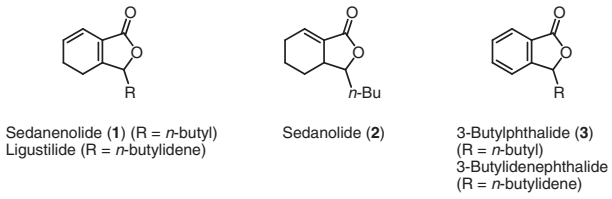
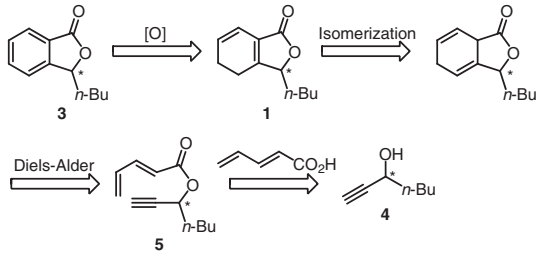


Fig. 1. Structures of Some Phthalides in Celery.

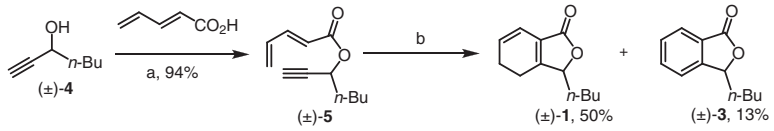


Scheme 1. Retrosynthetic Analysis.

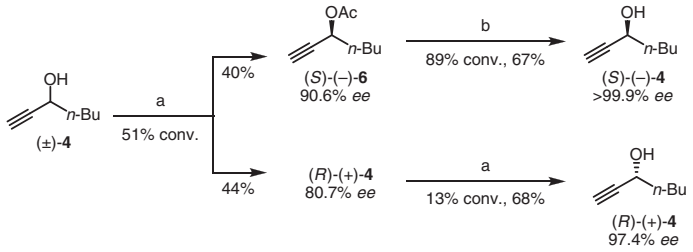
Table 1. Sensory Evaluation of Chiral **1** and **3**

Structure	Odor description[a]	Odor threshold[b]
(*S*)-(−)-**1**	Celery stem odor, strong, fresh, with aspects reminiscent of celery fibers.	0.14 ppm
(*R*)-(+)-**1**	Celery stem odor, bitter. Less intense in fresh celery odor than (*S*)-(−)-**1**.	0.60 ppm
(*S*)-(−)-**3**	Celery stem odor, strong, fresh, with aspects of celery leaf.	0.07 ppm
(*R*)-(+)-**3**	Celery stem odor, heavy, somewhat spicy. Less intense in fresh celery odor than (*S*)-(−)-**3**.	0.37 ppm

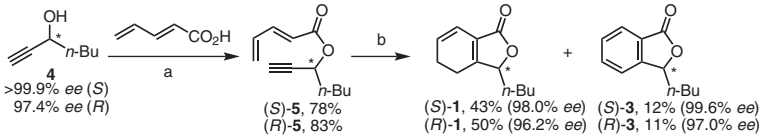
[a]Evaluated as a 10-ppm solution in water.
[b]Calculated from the result of a triangle test by 26 trained panelists.



Scheme 2.
Reagents and conditions: (a) PhCOCl, Et_3N, DMAP; (b) Δ, PhMe, 4,4-thiobis(6-*t*-butyl-*m*-cresol)



Scheme 3.
Reagents and conditions: (a) CAL-B, vinyl acetate, IPE; (b) CAL-B, 0.1 M phosphate buffer



Scheme 4.
Reagents and conditions: (a) PhCOCl, Et_3N, DMAP; (b) Δ, PhMe, 4,4-thiobis(6-*t*-butyl-*m*-cresol)

and ^{13}C-NMR at 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 rotation data were measured by a Jasco P-1030 polarimeter, and HRMS data were recorded with a Jeol JMS-700T (FAB) or Jeol JMS-T100LC AccuTOF (ESI) instrument. GCMS analyses were carried out with an Agilent 6890N gas chromatograph (30 m TC-1701 capillary column, 0.25 mm ID, 0.25 µm film) equipped with an Agilent 5973 mass selective detector. The enantiomeric excess was determined by gas chromatography, using a Chiramix® chiral separating column (60 m, 0.25 mm ID).[19] Analytical thin-layer chromatography (TLC) was carried out by 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).

*(S)-1-Heptyn-3-ol [(S)-(−)-**4**] and (R)-1-heptyn-3-ol [(R)-(+)-**4**].* A mixture of (±)-**4** (2.00 g, 17.8 mmol), CAL-B (Novozym 435, 0.18 g), diisopropyl ether (18 mL) and vinyl acetate (3.10 g, 35.6 mmol) was stirred at room temperature for 5 h. After filtration through a Celite® pad, the filtrate was concentrated *in vacuo*. The resulting residue was chromatographed on silica gel (150 g). Elution with *n*-hexane/ethyl acetate (50/1–5/1) gave acetate (*S*)-(−)-**6** (1.16 g, 40%, 90.6% *ee*) as a product and (*R*)-(+)-**4** (0.96 g, 44%, 80.7% *ee*) as a residual substrate. (*S*)-(−)-**6**. $[\alpha]_D^{20}$ −83.7 (*c* 1.08, CHCl$_3$); IR (film) cm^{-1}: 3293, 2958, 2934, 2866, 1743, 1468, 1372, 1233, 1049, 1020; ^{1}H-NMR (400 MHz, CDCl$_3$) δ: 0.91 (t, J = 7.2 Hz, 3H), 1.20–1.46 (m, 4H), 1.84–1.74 (m, 2H), 2.08 (s, 3H), 2.44 (d, J = 2.3 Hz, 1H), 5.33 (dt, J = 2.3, 6.7 Hz, 1H); ^{13}C-NMR (100 MHz, CDCl$_3$) δ: 13.87, 20.97, 22.17, 26.97, 34.25, 63.77, 73.34, 81.31, 169.94; HRMS (ESI): calcd. for $C_9H_{14}NaO_2$ $(M + Na)^+$, 177.0891; found, 177.0881.

A mixture of (*S*)-(−)-**6** (1.00 g, 6.2 mmol), CAL-B (Novozym 435, 0.10 g) and a 0.1 M phosphate buffer solution (pH 7.0, 20 mL) was stirred at room temperature for 3.5 h. After filtration through Celite®, the filtrate was extracted with diethyl ether, and the resulting extract was successively washed with an aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel (30 g), elution with *n*-hexane/ethyl acetate (50/1–5/1) giving (*S*)-(−)-**4** (0.49 g, 67%, >99.9% *ee*). $[\alpha]_D^{20}$ −9.74 (*c* 1.03, CHCl$_3$); IR (film) cm^{-1}: 3310, 2958, 2935, 2863, 1467, 1381, 1051, 1020, 656, 629; ^{1}H-NMR (400 MHz, CDCl$_3$) δ: 0.92 (t, J = 7.2 Hz, 3H), 1.31–1.49 (m, 4H), 1.65–1.78 (m, 2H), 1.87 (s, 1H), 2.46 (d, J = 2.0 Hz, 1H), 4.37 (dt, J = 2.0, 6.5 Hz, 1H); ^{13}C-NMR (100 MHz, CDCl$_3$) δ: 13.95, 22.30, 27.12, 37.32, 62.30, 72.80, 85.00; HRMS (ESI): calcd. for $C_7H_{12}NaO$ $(M + Na)^+$, 135.0786; found, 135.0777.

A mixture of (*R*)-(+)-**4** (0.84 g, 6.9 mmol, 80.7% *ee*), CAL-B (Novozym 435, 0.07 g), diisopropyl ether (7 mL) and vinyl acetate (1.20 g, 13.8 mmol) was stirred at room temperature for 6 h. After filtration through a Celite® pad, the filtrate was concentrated *in vacuo*. The resulting residue was chromatographed on silica gel (35 g), elution with *n*-hexane/ethyl acetate (50/1–5/1) giving residual (*R*)-(+)-**4** (0.55 g, 68%, 97.4% *ee*) as a colorless oil. $[\alpha]_D^{20}$ +9.34 (*c* 1.05, CHCl$_3$); HRMS (ESI): calcd. for $C_7H_{12}NaO$ $(M + Na)^+$, 135.0786; found, 135.0775. All other data were identical with those for (*S*)-(−)-**4**.

*1-Ethynylpentyl 2,4-pentadienoate [(±)-**5**].* To a mixture of 2,4-pentadienoic acid (0.60 g, 6.1 mmol) and toluene (3 mL) was added a mixture of benzoyl chloride (0.86 g, 6.1 mmol), triethylamine (0.62 g, 6.1 mmol) and toluene (3 mL) at 10 °C. After being stirred at room temperature for 0.5 h, the reaction mixture was filtered through a Celite® pad. The filtrate was concentrated *in vacuo* to give a crude anhydride (1.36 g).

To a mixture of this anhydride (1.36 g) and THF (3 mL) was added dropwise a mixture of (±)-**4** (0.30 g, 2.7 mmol), triethylamine (0.27 g, 2.7 mmol), a catalytic amount of *N*,*N*-dimethylaminopyridine and THF (3 mL) at 10 °C. After being stirred at room temperature for 0.5 h, the reaction mixture was diluted with diethyl ether, and successively washed with diluted aqueous hydrochloric acid, a saturated aqueous sodium bicarbonate solution and brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel (45 g) and eluted with *n*-hexane/ethyl acetate (50/1) to give (±)-**5** (0.48 g, 94%) as a colorless oil. IR (film) cm^{-1}: 2958, 1716, 1599, 1304, 1265, 1198, 1140, 1006, 866; ^{1}H-NMR (400 MHz, CDCl$_3$) δ: 0.92 (t, 3H, J = 7.1 Hz), 1.31–1.50 (m, 4H), 1.78–1.83 (m, 2H), 2.45 (d, 1H, J = 2.2 Hz), 5.43 (dt, 1H, J = 2.2, 6.7 Hz), 5.51 (d, 1H, J = 9.6 Hz), 5.63 (d, 1H, J = 17.0 Hz), 5.92 (d, 1H, J = 15.1 Hz), 6.46 (dt, 1H, J = 17.0, 10.6 Hz), 7.30 (dd, 1H, J = 15.6, 11.0 Hz); ^{13}C-NMR (100 MHz, CDCl$_3$) δ: 13.87, 22.19, 26.99, 34.34, 63.76, 73.39, 81.35, 121.53, 126.06, 134.62, 145.53, 165.68; HRMS (ESI): calcd. for $C_{12}H_{17}O_2$ $(M + H)^+$, 193.1229; found, 193.1229.

*(S)-1-Ethynylpentyl 2,4-pentadienoate [(S)-(−)-**5**].* In the same manner as that described for the synthesis of (±)-**5**, (*S*)-(−)-**4** (0.30 g, 2.67 mmol) afforded ester (*S*)-(−)-**5** (0.41 g, 78%) as a colorless oil. $[\alpha]_D^{20}$ −62.9 (*c* 1.02, CHCl$_3$); HRMS (ESI): calcd. for $C_{12}H_{16}NaO_2$ $(M + Na)^+$, 215.1048; found, 215.1050. All other data were identical with those for (±)-**5**.

*(R)-1-Ethynylpentyl 2,4-pentadienoate [(R)-(+)-**5**].* In the same manner as that described for the synthesis of (±)-**5**, (*R*)-(+)-**4** (0.30 g, 2.67 mmol) afforded ester (*R*)-(+)-**5** (0.43 g, 83%) as a colorless oil. $[\alpha]_D^{20}$ +60.3 (*c* 1.04, CHCl$_3$); HRMS (ESI): calcd. for $C_{12}H_{17}O_2$ $(M + H)^+$, 193.1229; found, 193.1228. All other data were identical with those for (±)-**5**.

*(±)-Sedanenolide [(±)-**1**] and (±)-3-butylphthalide [(±)-**3**].* A mixture of (±)-**5** (0.40 g, 2.0 mmol), toluene (40 mL) and a catalytic amount of 4,4-thiobis(6-*t*-butyl-*m*-cresol) was heated at 220 °C for 9 h in an autoclave under argon. The reaction mixture was concentrated *in vacuo*. The resulting residue was chromatographed on silica gel (15 g) and eluted with *n*-hexane/ethyl acetate (20/1–10/1) to give a mixture of (±)-**1** and (±)-**3** (0.27 g), together with a small amount of impurities, as a pale yellow oil. Further purification by Lobar® column chromatography [Merck LiChroprep® Si 60 (40–63 µm), pre-packed column size A (240–10), *n*-hexane/ethyl acetate (20/1)] gave (±)-**1** (0.19 g, 50%) and (±)-**3** (49 mg, 13%), both as colorless oils. (±)-**1**. IR (film) cm^{-1}: 2932, 1750, 1655, 1435, 1335, 1273, 1045, 1006, 963, 715; ^{1}H-NMR (400 MHz, CDCl$_3$) δ: 0.90 (t, 3H, J = 7.1 Hz), 1.29–1.44 (m, 4H), 1.53 (m, 1H), 1.88 (m, 1H), 2.43–2.52 (m, 4H), 4.92 (dd, 1H, J = 7.8, 3.7 Hz), 5.91 (m, 1H), 6.20 (d, 1H, J = 9.6 Hz); ^{13}C-NMR (100 MHz, CDCl$_3$) δ: 13.83, 20.77, 22.27, 22.42, 26.70, 31.88, 82.48, 116.87, 124.49, 128.28, 161.37, 171.24; GCMS: 192 (13, M^+), 135 (4), 107 (100), 91 (4), 85 (8), 77 (27), 57 (7), 51 (6), 41 (4); HRMS (ESI): calcd. for $C_{12}H_{16}NaO_2$ $(M + Na)^+$, 215.1048; found, 215.1046. (±)-**3**. IR (film) cm^{-1}: 2956, 1760, 1347, 1285, 1212, 1061, 984, 743, 708, 694; ^{1}H-NMR (400 MHz, CDCl$_3$) δ: 0.90 (t, J = 7.1 Hz, 3H), 1.30–1.50 (m, 4H), 1.76 (m, 1H), 2.05 (m, 1H), 5.47 (dd, J = 8.0, 3.9 Hz, 1H), 7.43 (d, J = 7.6 Hz, 1H), 7.52 (t, J = 7.6 Hz, 1H), 7.67 (t, J = 7.6 Hz, 1H), 7.89 (d, J = 7.6 Hz, 1H); ^{13}C-NMR (100 MHz, CDCl$_3$) δ: 13.83, 22.40, 26.85, 34.41, 81.42, 121.68, 125.69, 126.14, 128.99, 133.90, 150.10, 170.68; GCMS: 190 (2, M^+), 133 (100), 105 (27), 77 (12), 51 (5); HRMS (ESI): calcd. for $C_{12}H_{14}NaO_2$ $(M + Na)^+$, 213.0892; found, 213.0902.

*(S)-(−)-Sedanenolide [(S)-(−)-**1**] and (S)-(−)-3-butylphthalide [(S)-(−)-**3**].* In the same manner as that described for the synthesis of the racemates, (*S*)-(−)-**5** (0.35 g, 1.80 mmol) afforded (*S*)-(−)-**1** (0.15 g, 43%, 98.0% *ee*) and (*S*)-(−)-**3** (41 mg, 12%, 99.6% *ee*), both as colorless oils. (*S*)-(−)-**1**. $[\alpha]_D^{20}$ −134 (*c* 1.04, CHCl$_3$); HRMS (ESI): calcd. for $C_{12}H_{16}NaO_2$ $(M + Na)^+$, 215.1048; found, 215.1064. All other data were identical with those for (±)-**1**. (*S*)-(−)-**3**. $[\alpha]_D^{20}$ −69.1 (*c* 1.04, CHCl$_3$); HRMS (ESI): calcd. for $C_{12}H_{16}NaO_2$ $(M + Na)^+$, 213.0892; found, 213.0895. All other data were identical with those for (±)-**3**.

*(R)-(+)-Sedanenolide [(R)-(+)-**1**] and (R)-(+)-3-butylphthalide [(R)-(+)-**3**].* In the same manner as that described for the synthesis of the racemates, (*R*)-(+)-**5** (0.35 g, 1.80 mmol) afforded (*R*)-(+)-**1** (0.17 g, 50%, 96.2% *ee*) and (*R*)-(+)-**3** (37 mg, 11%, 97.0% *ee*), both as colorless oils. (*R*)-(+)-**1**. $[\alpha]_D^{20}$ +121 (*c* 1.02, CHCl$_3$); HRMS (ESI): calcd. for $C_{12}H_{17}O_2$ $(M + H)^+$, 193.1229; found, 193.1235. All other data were identical with those for (±)-**1**. (*R*)-(+)-**3**. $[\alpha]_D^{20}$ +64.8 (*c* 1.02, CHCl$_3$); HRMS (ESI): calcd. for $C_{12}H_{16}NaO_2$ $(M + Na)^+$, 213.0892; found, 213.0910. All other data were identical with those for (±)-**3**.

Sensory evaluation. Each synthetic sample was diluted with water to 10 ppm, and the odor of its headspace was evaluated by trained panelists. A defined amount of each synthetic compound dissolved in methanol (1%) was diluted with water step by step to give several concentrations. The initial concentration, which was dependent on the substance, was determined in preliminary experiments.

The odor detection threshold was determined by the triangle test,[20,21] using water as a blank. Each sample was presented to 26 trained panelists in order of decreasing concentration, and the threshold value was calculated as the average.

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