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SYNTHESIS OF (6S,1'S)-(+)-HERNANDULCIN, A SWEETNER, AND ITS STEREOISOMERS†

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Abstract -- All of the four possible stereoisomers of hernandulcin [6-(1'-hydroxy-1',5'-dimethyl-4'-hexenyl)-3-methyl-2-cyclohexenone] were synthesized starting from the enantiomers of limonene. The absolute configuration of the naturally occurring and sweet-tasting (+)-hernandulcin was established as 6S,1'S. Other stereoisomers were not sweet at all.

In 1985 Kinghorn and his coworkers isolated an extremely sweet bisabolene-type sesquiterpene from an aztec herb Lippia dulcis Trev. (Verbenaceae).[1] This plant was known to the Aztecs as Tzonpelic xihuitl (literally 'sweet herb') and was described in a book written between 1570~1576 by a Spanish physician F. Hernández.[1,2] Kinghorn et al. named the sesquiterpene (+)-hernandulcin, showed it to be more than 1,000 times as sweet as sucrose, and elucidated its structure as shown in **1'** including the relative stereochemistry as 6R*,1'R*. Its absolute configuration, however, remained unknown. In view of the intense sweetness of (+)-hernandulcin, we became interested in synthesizing all of the four possible stereoisomers of **1'** so that we could establish the absolute configuration of (+)-hernandulcin. Another purpose of the synthesis was to clarify the relationship between stereochemistry and taste. Herein we report in detail the synthesis of the stereoisomers of **1**, which resulted in the assignment of (6S,1'S)-configuration to (+)-hernandulcin.[3]

Our synthetic strategy as shown in the Scheme was to synthesize all of the four stereoisomers (**1**, **1'**, **2** and **2'**) of hernandulcin starting from the enantiomers of limonene **3**. In other words, the asymmetry at C-4 of limonene **3** was utilized to prepare hernandulcin stereoisomers with known absolute configuration at C-6. Both the enantiomers (**3** and **3'**) of limonene are commercially available.

First, (6R,1'R)-hernandulcin **1**, and (6R,1'S)-epihernandulcin **2** were synthesized from (S)-limonene **3**. Epoxidation of **3** with 2.2 eq of m-chloroperbenzoic acid (MCPBA) furnished **4** in 58.6 % yield as a stereoisomeric mixture. Treatment of **4** with prenylmagnesium chloride ($Me_2C{=}CHCH_2MgCl$) in the presence of CuI gave **5** in 80.0 % yield. The Grignard reagent selectively cleaved the less substituted epoxy ring of **4**. Ring-opening of the epoxide **5** with $PhSe^-$ was effected with PhSeNa in EtOH.[4] The product was chromatographed to give, in the order of elution, the less polar isomer of **6b** (8.1 % yield), a diastereo-

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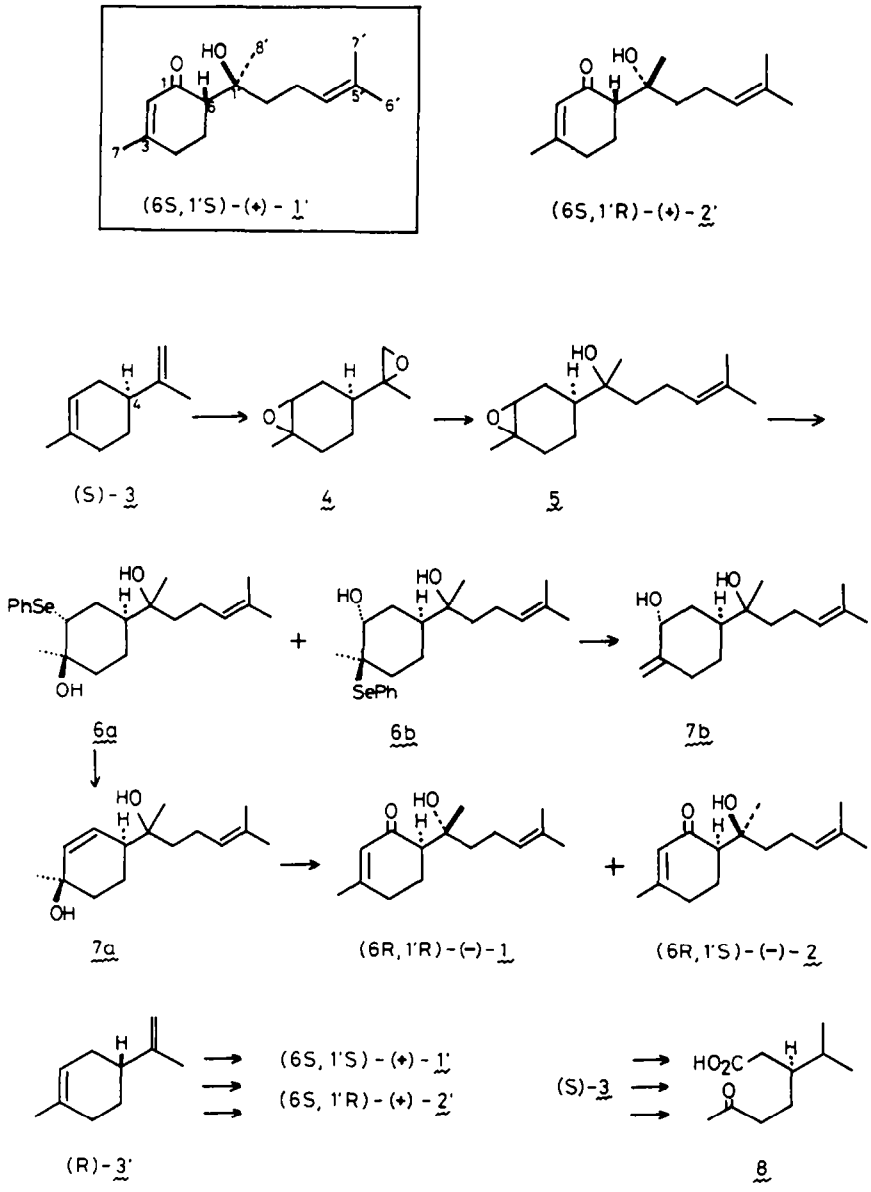

meric mixture of **6b** (12.6 %), the more polar isomer of **6b** (0.9 %), a mixture of the more polar isomer of **6b** and **6a** (17.6 %), and finally the desired diastereomeric mixture of **6a** (40.9 %). The structures assigned to **6b** and **6a** were supported by their conversion to **7b** and **7a**, respectively. When the less polar isomer of **6b** was treated with H_2O_2, a crystalline alcohol was obtained in 73.9 % yield. It showed only three Me signals (δ 1.10, 1.61, 1.66) in its NMR spectrum. The spectrum also revealed the presence of a $C=CH_2$ group (δ 4.65~4.85). The above NMR feature could best be explained by the structure **7b**. The OH group attached to the cyclohexane ring of **7b** was thought to be axial, because the NMR signal due to the eq CHOH was observed at δ 4.32 with $W_{1/2}$=7 Hz. The parent phenylselenide must therefore be **6b**. In **6b** the signal due to the eq CHOH was observed at δ 3.92 ($W_{1/2}$=9 Hz) in the case of the less polar isomer and at δ 3.95 ($W_{1/2}$=7 Hz) in the case of the more polar isomer, supporting the axial orientation of the OH group attached to the

ring. The trans-diaxial ring-opening of 5 with $PhSe^-$ demanded the PhSe group of **6b** to be axial, too. In the NMR spectrum of **6a**, the signal due to CHSePh was observed at δ 3.40 ($W_{1/2}$=7 Hz). The small $W_{1/2}$ value indicated the axial orientation of the PhSe group. The stereostructure of the cyclic part of **6a** was therefore assigned to be depicted in the formula, taking into account the trans-diaxial ring-cleavage of the epoxide **5**. Treatment of **6a** with H_2O_2 yielded a diastereomeric mixture of **7a** in 78.7 % yield. Its NMR spectrum clearly indicated the presence of four Me groups [δ 1.11 and 1.20 (total 3H), 1.26, 1.62, 1.68] and -CH=CH- olefinic protons (δ 5.70~5.90) in accord with the assigned structure **7a**.

The final step leading to hernandulcin stereoisomers was oxidation of **7a** with $CrO_3 \cdot C_5H_5N \cdot HCl$ (PCC).[5] The product was purified by chromatography to give the less polar oxidation product (6.2 % yield) and the more polar isomer (9.0 %), both as oils. The major product of the oxidation was an unidentified tarry material. Several other oxidation conditions were tried without any success. The ^1H- and ^{13}C NMR spectral properties of the less polar product coincided with those reported for (+)-hernandulcin.[1] Its structure must therefore be (6R,1'R)-**1**. The overall yield of **1** from **3** was 0.94 % in five steps. The synthetic (6R,1'R)-**1**, however, was levorotatory: $[\alpha]_D^{22}$ -117° (EtOH), while natural hernandulcin was dextrorotatory: $[\alpha]_D^{25}$ +109° (EtOH).[1] The absolute configuration of the dextrorotatory natural product was thus assigned to be 6S,1'S. The more polar isomer (6R,1'S)-**2**, $[\alpha]_D^{22}$ -133° (EtOH), was named (-)-epihernandulcin. Inspection of the molecular models of **1** and **2** revealed the ready formation of an intramolecular H-bond between C=O and OH groups in the case of **1**, because of the adoption of the eq orientaion by $Me_2C=CH(CH_2)_2$- group attached to the six-membered ring newly generated by the H-bonding. The H-bonding made **1** less polar than **2**. The presence of the H-bonding in **1** could also be demonstrated by the CD measurement of **1** and **2**. In the CD spectrum of **2**, where H-bonding is unfavorable, a single minimum was observed at 230 nm ($[\theta]_{230}^{22}$ -2.95 x 10^7). On the other hand, **1** showed a maximum at 215 nm ($[\theta]_{215}^{22}$ -5.14 x 10^6) and a minimum at 230 nm ($[\theta]_{230}^{22}$ -8.85 x 10^6). The former maximum was probably due to the H-bonded form and the latter to the non H-bonded form. Similar influence of H-bonding on the shape of CD spectrum had been observed by Legrand and Rougier in the case of a steroid.[6]

We next turned our attention to the synthesis of natural hernandulcin itself starting from (R)-(+)-limonene **3'**. In the same manner as described above, **7a'** was prepared from **3'** via **4'**, **5'** and **6a'**. Oxidation of **7a'** with PCC afforded (6S,1'S)-(+)-hernandulcin **1'**, $[\alpha]_D^{22}$ +126° (EtOH) (lit[1] +109°), in 5.6 % yield. The overall yield of **1'** from **3'** was 1.1 % in five steps. (6S,1'R)-(+)-Epihernandulcin **2'** $[\alpha]_D^{15}$ +141° (EtOH), was also obtained in 6.6 % yield from **7a'**. The CD spectra of **1'** and **2'** were antipodal to those of **1** and **2**, respectively.

Before carrying out the sensory test of the four stereoisomers of hernandulcin, efforts were made to establish the enantiomeric purity of limonene enantiomers (**3** and **3'**) and that of hernandulcin enantiomers (**1** and **1'**). By the method previously reported by us, (R)-(+)-**3'** was proved to be of 98 % e.e.[7] In the case of (S)-(-)-limonene **3**, it was converted to **8** by partial hydrogenation and ozonolysis followed by oxidative workup with CrO_3, and (R)-α-(1-naphthyl)ethylamide of **8** was analyzed by HPLC to reveal **8**, hence **3**, to be of 88 % e.e. The enantiomeric purity of (6S,1'S)-(+)-hernandulcin **1'** derived from **3'** (98 % e.e.) was estimated to be 97 % e.e. by measuring its 400 MHz ^1H NMR spectrum in the presence of 23 mol % of a chiral shift reagent $Eu(hfbc)_3$ in C_6D_6. In the same manner, (6R,1'R)-**1** derived from **3** (88 % e.e.) was found to be of 92 % e.e. The discrepancy between the enantiomeric purity of **3** and that of **1** might be due to experimental errors.

The sensory tests of **1**, **1'**, **2** and **2'** were carried out at Ajinomoto Co., Ltd. by the courtesy of Dr. T. Ichikawa. (6S,1'S)-(+)-Hernandulcin **1'** was about 1,100~1,200 times as sweet as sucrose with some bitter taste. Other stereoisomers **1**, **2** and **2'** were all bitter and somewhat pungent with no perceptible sweet taste. The naturally occurring

hernandulcin was the only stereoisomer with sweet taste.

In conclusion, the absolute configuration of (+)-hernandulcin was definitely proved to be 6S,1'S.

EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra were measured as films for oils or as nujol mulls for solids on a Jasco IRA-102 spectrometer. NMR spectra were recorded with TMS as an internal standard at 60 MHz on a Hitachi R-24A spectrometer or at 100 MHz on a JEOL JNM FX-100 spectrometer or at 400 MHz on a JEOL JNM FX-400 spectrometer or at 500 MHz on a Bruker AM-500 spectrometer. Optical rotations were measured on a Jasco DIP 140 polarimeter. Mass spectra were recorded on a JEOL DX-303 spectrometer at 70 eV. CD spectra were measured on a Jasco J-20C spectropolarimeter. UV spectra were measured on a Hitachi U-3200 spectrophotometer. Fuji gel BW-820 MH was used for SiO_2 column chromatography.

(4S)-(-)-1,2,8,9-Diepoxy-p-menthane **4**. To a stirred and ice-cooled mixture of (-)-limonene **3** [$[\alpha]_D^{22}$ -105° (neat, d_4^{22} 0.8376); 3.00 g, 22.1 mmol] in dry CH_2Cl_2 (120 ml) and sat $NaHCO_3$ soln (80 ml) was added portionwise 80 % MCPBA (10.4 g, 48.1 mmol). The mixture was stirred at 0° for 9 h. Then 10 % $NaHSO_3$ soln (10 ml) was added to the mixture. The organic layer was separated and the aq layer was extracted with CH_2Cl_2. The combined organic soln was washed with 10 % Na_2CO_3 soln and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by SiO_2 chromatography [30 g; n-hexane-ether (8:1~6:1)] and distillation to give **4** (2.17 g, 58.6 %), b.p. 81°/3 Torr; n_D^{20} 1.4648; $[\alpha]_D^{20}$ -44.9° (c=3.00, Et_2O); νmax 3050 (w), 905 (m), 855 (s), 840 (m), 800 (m), 765 (m) cm^{-1}; δ ($CDCl_3$) 1.20 (0.5 x 3H, s), 1.22 (0.5 x 3H, s), 1.29 (3H, s), 1.35~2.00 (7H, m), 2.48~2.58 (2H, m), 2.88~3.08 (1H, m). MS: m/z 168 (M^+), 153 (M^+-15). (Found: C, 71.01; H, 9.48. Calc for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59 %).

Determination of the optical purity of (-)-**3**. (S)-3-Isopropyl-6-oxoheptanoic acid **8** obtained from (-)-limonene **3** was treated with (R)-α-(1-naphthyl)ethylamine in dry CH_2Cl_2 in the presence of DCC to give the corresponding (R)-amide; HPLC [Column, Nucleosil® 50-5, 25 cm x 4.6 mm; Solvent, n-hexane-THF (2:1), 1.3 ml/min; Detected at 254 nm] Rt 8.6 min [(R)-amide of (S)-**8**, 93.8 %] and 13.1 min [(R)-amide of (R)-**8'**, 6.2 %]. In the same manner, (S)-amide of **8** was prepared and analyzed under the same condition; Rt 8.7 min [(S)-amide of (R)-**8'**, 5.9 %] and 12.1 min [(S)-amide of (S)-**8**, 94.1 %]. The optical purity of (-)-**3** was therefore ~88 % e.e.

(4R)-(+)-1,2,8,9-Diepoxy-p-menthane **4'**. In the same manner as described for **4**, (+)-limonene **3'** ($[\alpha]_D^{19}$ +126° (neat, d_4^{19} 0.8865); 98.1 % e.e.; 20.2 g, 147 mmol) gave **4'** (18.0 g, 72.9 %), b.p. 76~78°/2.5 Torr; n_D^{22} 1.4616; $[\alpha]_D^{22}$ +50.1° (c=2.99, Et_2O); The IR, NMR and mass spectra of **4'** were identical with those of **4**. (Found: C, 71.04; H, 9.45. Calc for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59 %).

(1'S)-6-Methyl-2-(3',4'-epoxy-4'-methylcyclohexyl)-5-hepten-2-ol **5**. A Grignard reagent was prepared from 4-chloro-2-methyl-2-butene (19.0 g, 182 mmol) and Mg (13.3 g, 547 mg atom) in dry THF (250 ml), employing a catalytic amount of 1,2-dichloroethane as an initiator. To a stirred and cooled mixture of **4** (12.0 g, 71.4 mmol) and CuI (1.8 g, 9.5 mmol) in dry THF (300 ml) was added dropwise the Grignard reagent over 15 min at -25° under Ar and the resulting mixture was stirred at -25° for 30 min. It was then poured into sat NH_4Cl soln and filtered to remove the insoluble material. The filtrate was extracted with ether and the ether soln was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (400 g). Elution with n-hexane-ether (8:1) gave **4** (2.26 g, 18.8 %). Further elution with n-hexane-ether (6:1~2:1) gave **5** (11.0 g, 80.0 % based on the consumed **4**) as a colorless oil, νmax 3470 (s), 1180 (m), 1120 (s), 1020 (m), 840 (m) cm^{-1}; δ ($CDCl_3$) 1.08 (3H, s), 1.31 (3H, s), 1.62 (3H, s), 1.68 (3H, s), 1.20~2.20 (12H, m), 2.90~3.10 (1H, m), 5.12 (1H, t, J=6 Hz); MS m/z 238 (M^+), 220 (M^+-18). This was employed in the next step without further purification.

(1'R)-6-Methyl-2-(3',4'-epoxy-4'-methylcyclohexyl)-5-hepten-2-ol **5'**. In the same manner as described for **5**, **4'** (6.60 g, 39.3 mmol) gave **5'** (7.48 g, 84.1% based on the 95.2 % consumption of **4'**) as a colorless oil. The IR, NMR and mass spectra of **5'** were identical with those of **5**.

(1R,2R,4S)-4-(1'-Hydroxy-1',5'-dimethyl-4'-hexenyl)-1-methyl-2-phenylselenocyclohexanol **6a** and (1R,2R,5S)-5-(1'-hydroxy-1',5'-dimethyl-4'-hexenyl)-2-methyl-2-phenylselenocyclohexanol **6b**. To a stirred and ice-cooled suspension of $(PhSe)_2$ (72.0 g, 231 mmol) in dry EtOH (1000 ml) was added portionwise $NaBH_4$ (18.0 g, 476 mmol) under N_2 stream. **5** (11.0 g, 46.2 mmol) was added to the resulting colorless soln and the mixture was heated under reflux for 4 h. It was then concentrated in vacuo to remove about a half volume of the solvent and diluted with sat NH_4Cl soln. The mixture was extracted with EtOAc and the EtOAc soln was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was repeatedly chromatographed over SiO_2 (2900 g in total). The first fraction eluted with $CHCl_3$ gave the less polar isomer of **6b** (1.48 g, 8.1%). This was purified by recrystallization from EtOAc-MeOH (6:1) to give colorless needles, m.p. 151~152°; $[\alpha]_D^{23}$ -28.3° (c=0.99, dioxane); νmax 3370 (s,sh), 3300 (s), 3080 (w), 1580 (w), 1475 (m), 1205 (w), 1180 (m), 1160 (m), 1120 (m), 1080 (w), 1025 (s), 1005 (s), 960 (m), 925 (m), 875 (w), 825 (m), 740 (s), 695 (s) cm^{-1}; δ (100 MHz, $CDCl_3$) 1.20 (3H, s), 1.35 (3H, s), 1.58 (2H, s, OH), 1.65 (3H, br.s), 1.70 (3H, br.s), 1.40~2.25 (11H, m), 3.92 (1H, m, $W_{1/2}$=9 Hz), 5.16 (1H, br.t, J=6 Hz), 7.05~7.70 (5H, m); MS m/z 396 (M^++1).

The second fraction eluted with $CHCl_3$ gave a diastereomeric mixture of **6b** (2.30 g, 12.6 %) as a solid. The third fraction eluted with $CHCl_3$ gave the more polar isomer of **6b** (0.17 g, 0.9 %) as a pale yellow oil. This slowly solidified at room temp, m.p. 62~63°; $[\alpha]_D^{22}$ -43.7° (c=1.02, dioxane); νmax 3420 (s), 3060 (w), 1575 (w), 1160 (m), 1120 (s), 1080 (m), 1020 (s), 1010 (s), 950 (w), 915 (w), 870 (m), 740 (s), 690 (s) cm^{-1}; δ (100 MHz, $CDCl_3$) 1.20 (3H, s), 1.36 (3H, s), 1.65 (3H, br.s), 1.70 (3H, br.s), 1.40~2.30 (13H, m), 3.95 (1H, m, $W_{1/2}$=7 Hz), 5.16 (1H, br.t, J=6 Hz), 7.15~7.70 (5H, m); MS m/z 396 (M^++1), 378 (M^++1-18).

The fourth fraction eluted with $CHCl_3$ gave a mixture of the more polar isomer of **6b** and **6a** (3.22 g, 17.6 %). The fifth fraction eluted with $CHCl_3$-MeOH (100:1) gave **6a** (7.46 g, 40.9 %) as a pasty oil, νmax 3420 (s), 3060 (w), 1575 (w), 1475 (w), 1170 (s), 1100 (s), 1020 (m), 980 (m), 905 (m), 845 (w), 820 (w), 735 (s), 690 (s) cm^{-1}; δ ($CDCl_3$) 1.05 (0.5 x 3H, s), 1.08 (0.5 x 3H, s), 1.39 (3H, s), 1.61 (3H, br.s), 1.66 (3H, br.s), 1.25~2.20 (13H, m), 3.40 (1H, m, $W_{1/2}$=7 Hz),

5.08 (1H, br.t, J=6.5 Hz), 7.10~7.70 (5H, m); MS m/z 396 (M^++1), 378 (M^++1-18) TLC (Merck Kieselgel 60 F_{254} Art 5715; developed with $CHCl_3$-MeOH=20:1): Rf 0.45 (the less polar isomer of **6b**), 0.42 (the more polar isomer of **6b**) and 0.40 (**6a**).

(1S,2S,4R)-4-(1'-Hydroxy-1',5'-dimethyl-4'-hexenyl)-1-methyl-2-phenylselenocyclohexanol **6a'**. In the same manner as described for **6a**, **5'** (11.0 g, 46.2 mmol) gave **6a'** (7.08 g, 38.8 %) as a pasty oil. In this case, **6b'** was not purified. The IR, NMR and mass spectra of **6a'** were identical with those of **6a**.

(1'S,3'R)-2-(3'-Hydroxy-4'-methylenecyclohexyl)-6-methyl-5-hepten-2-ol **7b**. To a stirred and ice-cooled soln of the less polar isomer of **6b** (200 mg, 0.506 mmol) in THF (8 ml) was added 35 % H_2O_2 soln (0.49 g, 5.04 mmol). The mixture was gradually warmed to room temp over 1 h and the stirring was continued for 2 h at room temp. It was then diluted with sat $NaHCO_3$ soln and extracted with EtOAc. The EtOAc soln was washed with 10 % Na_2CO_3 soln and brine, dried (K_2CO_3) and concentrated in vacuo. The residue was chromatographed over neutral Al_2O_3 (grade 4, 11 g). Elution with n-hexane-EtOAc (8:1) gave **7b** (89 mg, 73.9 %) as crystals, m.p. 65~67°; $[\alpha]_D^{22}$ -44.6° (c=1.05, Et_2O); vmax 3370 (s), 3080 (w), 1650 (w), 1240 (m), 1145 (m), 1090 (s), 1070 (s), 1040 (s), 985 (s), 900 (s), 880 (m) cm^{-1}; δ ($CDCl_3$) 1.10 (3H, s), 1.61 (3H, br.s), 1.66 (3H, br.s), 1.20~2.35 (13H, m), 4.32 (1H, br.s, $W_{1/2}$=7 Hz), 4.65~4.85 (2H, m), 5.10 (1H, br.t, J=6 Hz); MS: m/z 220 (M^+-18); (Found: C, 75.32; H, 10.95. Calc for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00 %).

(1'S,4'R)-2-(4'-Hydroxy-4'-methyl-2'-cyclohexenyl)-6-methyl-5-hepten-2-ol **7a**. To a stirred and ice-cooled soln of **6a** (500 mg, 1.27 mmol) in THF (20 ml) was added 35 % H_2O_2 soln (1.2 g, 12.4 mmol). The mixture was gradually warmed to room temp over 1 h and the stirring was continued for 5 h at room temp. The work-up of the mixture was followed by chromatographic purification in the same manner as described for **7b** to give 273 mg (78.7 %) of **7a** as a pale yellow oil, vmax 3400 (s), 3020 (w), 1640 (w), 1170 (m), 1115 (s), 900 (s), 790 (w), 735 (m) cm^{-1}; δ ($CDCl_3$) 1.11 (0.5 x 3H, s), 1.20 (0.5 x 3H, s), 1.26 (3H, s), 1.62 (3H, br.s), 1.68 (3H, br.s), 1.40~2.60 (11H, m), 5.13 (1H, br.t, J=6 Hz), 5.70~5.90 (2H, m); MS m/z 220 (M^+-18), 202 (M^+-36).

(1'R,4'S)-2-(4'-Hydroxy-4'-methyl-2'-cyclohexenyl)-6-methyl-5-hepten-2-ol **7a'**. In the same manner as described for **7a**, **6a'** (6.31 g, 16.0 mmol) gave **7a'** (3.12 g, 82.1 %). The IR, NMR and mass spectra of **7a'** were identical with those of **7a**.

(6S,1'S)-(+)-6-(1'-Hydroxy-1',5'-dimethyl-4'-hexenyl)-3-methyl-2-cyclohexenone [(+)-Hernandulcin] **1'** and its (6S,1'R)-(+)-isomer [(+)-epihernandulcin] **2'**. To a stirred suspension of $CrO_3 \cdot C_5H_5N \cdot HCl$ (PCC) (11.4 g, 52.9 mmol) in dry CH_2Cl_2 (200 ml) was added a soln of **7a'** (3.12 g, 13.1 mmol) in dry CH_2Cl_2 (50 ml). The mixture was stirred for 1.5 h at room temp. It was then diluted with ether and filtered through a short pad of Florisil (60 g). The filtrate was concentrated in vacuo and the residue was chromatographed over SiO_2 (40 g). Elution with n-hexane-ether (15:1) gave crude **1'** and crude **2'**, respectively. **1'** and **2'** were further chromatographed over Merck Lobar® column (Grosse B). Elution with n-hexane-ether (15:1) gave 173 mg (5.6 %) of **1'** as a pale yellow oil. A small portion of **1'** was distilled to give an analytical sample, b.p. 130~140° (bath temp)/0.09 Torr; n_D^{20} 1.4988; $[\alpha]_D^{22}$ +126° (c=0.113, EtOH); UV (c=0.0444, EtOH) λmax 236 nm (ε=13200); CD (c=0.200 g/l, n-hexane) $[\theta]_{330}^{22}$ +8.85 x 10^6, $[\theta]_{215}^{22}$ +5.20 x 10^6; vmax 3480 (m), 3050 (w,sh), 3000 (s), 2950 (s), 2870 (m), 1645 (s), 1215 (m), 1125 (m), 1020 (m), 1000 (m), 945 (m), 880 (m) cm^{-1}; δ (500 MHz, $CDCl_3$) 1.19 (3H, s), 1.49 (2H, ddd, J=8.4, 8.4 and 1.2 Hz), 1.64 (3H, s), 1.69 (3H, s), 1.69 (1H, m), 1.98 (3H, s), 2.04 (1H, m), 2.07 and 2.18 (2H, ddt, J=14.6, 7.2 and 8.4 Hz), 2.32 (1H, ddd, J=18.5, 5.0 and 2.5 Hz), 2.38 (1H, dm, J=13.0 Hz), 2.43 (1H, dd, J=14.1 and 14.5 Hz), 5.13 (1H, tm, J=7.2 Hz), 5.26 (1H, s), 5.89 (1H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 17.7, 21.6, 23.7, 24.1, 25.2, 25.8, 31.4, 40.3, 52.3, 74.0, 124.6, 127.7, 131.6, 163.5, 204.2; MS: m/z 236 (M^+, 1.5 %), 218 (M^+-18, 5 %), 110 (67 %), 95 (26 %), 82 (100 %); HRMS: m/z 236.1814. Calcd for $C_{15}H_{24}O_2$: 236.1776; HPLC: (Column, Nucleosil® 50-5, 25 cm x 4.6 mm; Solvent, n-hexane-i-PrOH=160:1; Flow rate, 0.66 ml/min; Detected at 254 nm) Rt 20.1 min (single peak); (Found: C, 76.11; H, 10.19. Calc for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23 %).

Further elution with n-hexane-ether gave 204 mg (6.6 %) of **2'** as a pale yellow oil, $[\alpha]_D^{15}$ +141° (c=0.111, EtOH); UV (c=0.0441, EtOH) λmax 236 nm (ε=13300); CD (c=0.200 g/l, n-hexane) $[\theta]_{330}^{22}$ +3.60 x 10^7; vmax 3470 (m), 3050 (w,sh), 3000 (s), 2950 (s), 2870 (m), 1645 (s), 1215 (s), 1190 (m), 1120 (m), 1085 (m), 1020 (m), 935 (m), 880 (m) cm^{-1}; δ (500 MHz, $CDCl_3$) 1.19 (3H, s), 1.39 and 1.56 (2H, ddd, J=13.0, 13.0 and 4.6 Hz), 1.60 (3H, s), 1.66 (3H, s), 1.96 (3H, s), 2.00 (2H, m), 2.06 (2H, m), 2.34 (2H, m), 2.35 (1H, dd, J=14.1 and 4.5 Hz), 5.03 (1H, s), 5.09 (1H, t, J=7.2 Hz), 5.85 (1H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 17.6, 22.1, 24.1, 25.1, 25.4, 25.7, 31.5, 37.0, 55.3, 74.4, 124.8, 127.5, 131.4, 163.5, 203.6; MS: m/z 236 (M^+, 4.5 %), 218 (M^+-18, 19 %), 110 (100 %), 95 (44 %), 82 (83 %); HRMS: m/z 236.1761. Calcd for $C_{15}H_{24}O_2$: 236.1776; (6S,1'S)-**1'** and (6S,1'R)-isomer **2'** were readily separable on TLC (Merck Kieselgel 60 F_{254} Art 5715; developed with n-hexane-ether 1:1): Rf 0.50 [(6S,1'S)-**1'**], 0.28 [(6S,1'R)-isomer **2'**].

(6R,1'R)-(-)-6-(1'-Hydroxy-1',5'-dimethyl-4'-hexenyl)-3-methyl-2-cyclohexenone [(-)-Hernandulcin] **1** and its (6R,1'S)-(-)-isomer [(-)-epihernandulcin] **2**. In the same manner as described for **1'** and **2'**, **7a** (2.01 g, 8.45 mmol) gave **1** (123 mg, 6.2 %) as a colorless oil and **2** (179 mg, 9.0 %) as a yellow oil. The physical data of **1** are as follows: b.p. 90~110° (bath temp)/0.05 Torr; n_D^{22} 1.4982; $[\alpha]_D^{22}$ -117° (c=0.112, EtOH); UV (c=0.0444, EtOH) λmax 236 nm (ε=13500); CD (c=0.200 g/l, n-hexane) $[\theta]_{330}^{22}$ -8.85 x 10^6, $[\theta]_{215}^{22}$ -5.14 x 10^6; The IR, ^1H NMR, ^{13}C NMR and mass spectra of **1** were identical with those of **1'**. HRMS: m/z 236.1745. Calcd for $C_{15}H_{24}O_2$: 236.1776. The physical data of **2** are as follows: $[\alpha]_D^{22}$ -133° (c=0.108, EtOH); UV (c=0.0441, EtOH) λmax 236 nm (ε=12900); CD (c=0.200 g/l, n-hexane) $[\theta]_{330}^{22}$ -2.95 x 10^7; The IR, ^1H NMR, ^{13}C NMR and mass spectra of **2** were identical with those of **2'**. HRMS: m/z 236.1750. Calcd for $C_{15}H_{24}O_2$: 236.1776.

Determination of the optical purity of **1** and **1'**. 400 MHz ^1H NMR of **1** in C_6D_6 was measured in the presence of 23 mol % of Eu(hfbc)$_3$, δ for C-2 H: 5.96 (96 %) and 6.20 (4 %). The optical purity of **1** was therefore 92 % e.e. **1'** was analyzed under the same condition. δ for C-2 H: 5.79 (1.5 %) and 6.11 (98.5 %). The optical purity of **1'** was therefore 97 % e.e.

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