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SYNTHESIS AND ABSOLUTE CONFIGURATION OF (+)-HERNANDULCIN, A NEW SESQUITERPENE WITH INTENSELY SWEET TASTE

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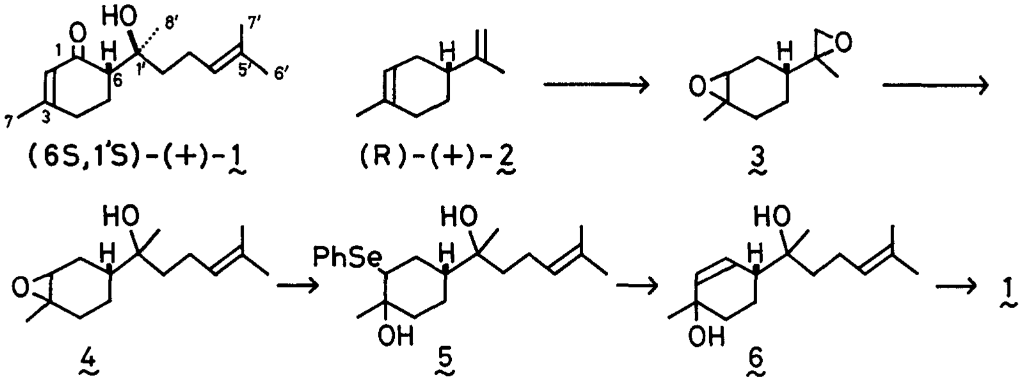
Summary: The absolute configuration of (+)-hernandulcin [6-(1',5'-dimethyl-1'-hydroxy-4'-hexenyl)-3-methyl-2-cyclohexenone] was shown to be 6*S*,1'*S* by synthesizing it from (*R*)-(+)-limonene.

Recently 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 Francisco Hernández.[1,2] Kinghorn *et al.* named the sesquiterpene (+)-hernandulcin, showed it to be more than 1000 times as sweet as sucrose, and elucidated its structure as shown in **1** including the relative stereochemistry. Its absolute configuration, however, remained unknown. In view of the intense sweetness of **1**, we thought it worth while to clarify its absolute configuration. Our strategy as shown in the Scheme was to synthesize (6*S*,1'*S*)-hernandulcin **1** starting from (*R*)-(+)-limonene **2**.

(*R*)-(+)-Limonene **2**[3] in CH_2Cl_2 was treated with 2.2 eq of *m*-$ClC_6H_4CO_3H$ at 0° for 4 hr to give **3** (72.9 %),[4] bp 76~78°/2.5 Torr; $[\alpha]_D^{22}$ +50.1° (c=2.99, ether), as a diastereomeric mixture. Treatment of **3** with $Me_2C{=}CHCH_2MgCl$ (prepared from 2.1 eq of $Me_2C{=}CHCH_2Cl$ and an excess of Mg in THF) and CuI (0.13 eq) at -30~-25° for 1 hr yielded **4** (84.1 %). Cleavage of the epoxy ring of **4** with $PhSe^-$ was effected with PhSeNa (prepared from 5 eq of Ph_2Se_2 and 10 eq of $NaBH_4$) in refluxing EtOH (4 hr)[5] to give **5** (38.8 % after SiO_2 chromatography) as a diastereomeric mixture. Treatment of **5** with 11.2 eq of 35 % H_2O_2 in THF at 0~20° for 10 hr gave **6** (82.1 % after Al_2O_3 chromatography) as a diastereomeric mixture. Finally oxidation of **6** (3.12 g) with 4 eq of $CrO_3 \cdot C_5H_5N \cdot HCl$ (PCC)[6] in CH_2Cl_2 for 1.5 hr at room temp yielded an oily mixture of products, which was chromatographed over SiO_2. The fractions containing (6*S*,1'*S*)-**1** and its (6*S*,1'*R*)-isomer was further chromatographed over Merck Lobar® column (Grösse B). Elution with *n*-hexane-ether (30:1~15:1) gave the less polar isomer as an oil (173 mg, 5.6 %). Further elution yielded the more polar isomer (204 mg, 6.6 %). The spectral data[7] of the less polar isomer, bp 130~140° (bath temp)/0.09 Torr; n_D^{20} 1.4988, were in excellent accord with the published data[1] of (+)-hernandulcin. The less polar isomer was thus (6*S*,1'*S*)-**1**.[8] Our synthetic (6*S*,1'*S*)-**1** was dextrorotatory: $[\alpha]_D^{20}$ +122° (c=0.111, EtOH).[9] Since the natural hernandulcin was also dextrorotatory [lit.[1] $[\alpha]_D^{25}$ +109° (c=0.11, EtOH)], its absolute configuration was established as



(6S,1'S)-(+)-1 (R)-(+)-2 3 4 5 6 → 1

6*S*,1'*S*.[10] Synthesis and sensory testings of all of the stereoisomers of **1** will be reported in due course.

References and Footnotes

1) C. M. Compadre, J. M. Pezzuto, A. D. Kinghorn and S. K. Kamath, *Science*, **227**, 417 (1985).
2) a) *Chem. Brit.*, 330 (1985). b) *Chem. and Eng. News*, January 28, p. 37 (1985).
3) The optical purity of (*R*)-(+)-**2**, $[\alpha]_D^{19}$ +126° (neat, d_4^{19}=0.8865), was estimated as 98.1 % in connection with our recently completed work on the synthesis of (-)-periplanone-B.
4) Correct spectral and analytical (MS or combustion) data were obtained for **3**, **4**, **5** and **6**.
5) K. B. Sharpless and R. F. Lauer, *J. Am. Chem. Soc.*, **95**, 2697 (1973).
6) E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 2647 (1975).
7) The spectral and analytical data of (6*S*,1'*S*)-**1** are as follows; IR νmax (film) 3490 (m), 3050 (w,sh), 3000 (s), 2950 (s), 2890 (m), 1645 (s), 1215 (s) cm^{-1}; UV (c=0.0444, EtOH) λmax 236 nm (ε=13200); ^1H NMR (500 MHz, $CDCl_3$) δ 1.18 (3H, s), 1.48 (2H, ddd, J=8.4, 8.4, 1.2 Hz), 1.63 (3H, s), 1.68 (3H, d, J=1.0 Hz), 1.69 (1H, m), 1.97 (3H, s), 2.03 (1H, m), 2.06 and 2.17 (2H, ddt, J=14.6, 7.2, 8.4 Hz), 2.31 (1H, ddd, J=18.5, 5.0, 2.5 Hz), 2.37 (1H, dm, J=13.0 Hz), 2.42 (1H, dd, J=14.1, 4.5 Hz), 5.12 (1H, tm, J=7.2 Hz), 5.26 (1H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 17.7, 21.6, 23.6, 24.1, 25.2, 25.8, 31.4, 40.2, 52.2, 73.9, 124.6, 127.6, 131.5, 163.5, 204.1; MS (*m*/*z*) 236 (M^+, 1.5 %), 218 (M^+-18, 5 %), 110 (67 %), 95 (26 %), 82 (100 %); 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. Calcd. for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23 %. (6*S*,1'*S*)-**1** was indeed very sweet.
8) (6*S*,1'*S*)-**1** and its (6*S*,1'*R*)-isomer were readily separable on TLC (Merck Kieselgel 60 F_{254} Art 5715; developed with *n*-hexane-ether 1:1): Rf 0.50 [(6*S*,1'*S*)-**1**], 0.28 [(6*S*,1'*R*)-isomer].
9) The optical purity of (6*S*,1'*S*)-**1** was estimated to be 94 % by measuring its ^1H NMR spectrum (400 MHz, C_6D_6) in the presence of 23 mol % of Eu(hfbc)$_3$.
10) Financial support of this work by Ajinomoto Co., Ltd. is gratefully acknowledged.

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