602 © 1989 The Chemical Society of Japan NOTES Bull. Chem. Soc. Jpn., 62, 602—604 (1989) [Vol. 62, No. 2

Synthesis of (±)-Hernandulcin by an Intramolecular Nitrile Oxide Cycloaddition Route from Farnesol

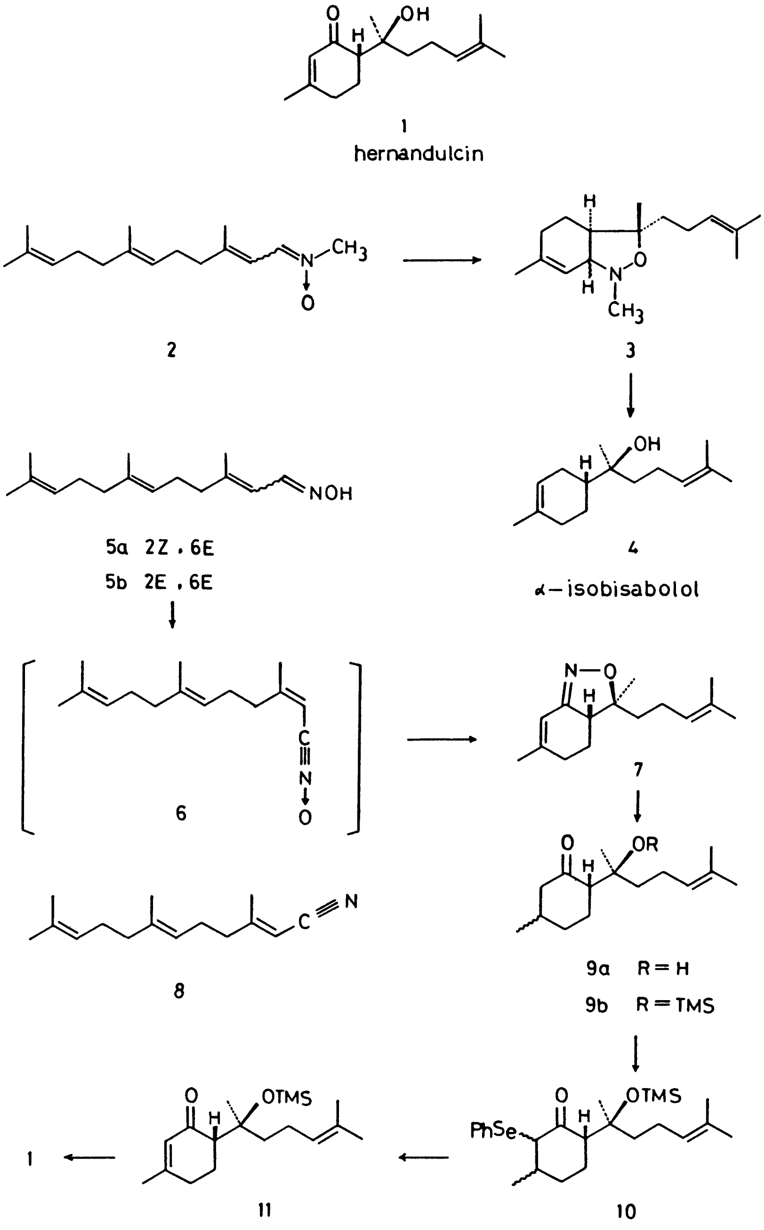
Guo-Chi ZHENG and Hiroshi KAKISAWA*
Department of Chemistry, University of Tsukuba, Tsukuba, Ibaraki 305

(Received June 28, 1988)

Synopsis. An intramolecular addition reaction of the nitrile oxide derived from (2*Z*, 6*E*)-farnesal oxime afforded an isoxazoline derivative, which was converted into hernandulcin, a sweet sesquiterpene of Verbenaceae plant.

Hernandulcin was found as a strongly sweet sesquiterpene from the Mexican plant *Lippia dulcis* Trev. (Verbenaceae) by Kinghorn[1)] according to a classic book written in 1570—1576 by a Spanish physician, F. Hernandez, about natural history of ancient Mexico. Hernandez described a remarkably sweet plant known to the Aztec people by the name *Tzonpelic xihuitl* (literally 'sweet herb').[2)] The structure and relative stereochemistry of this sesquiterpene **1** were proposed by Kinghorn[1)] and the absolute configuration was determined by Mori et al. by a synthesis.[3)] This report describes a convenient synthesis of (±)-hernandulcin from farnesol via an intramolecular nitrile oxide cycloaddition route.

Previously, the author reported that a nitrone **2** derived from (6*E*)-farnesal afforded a cycloaddition product **3** which was convertible into α-isobisabolol



(**4**).[4] Although the relative stereochemistry of isoxazoline intermediate **3** was the same as that of hernandulcin, several attempts failed in converting the intermediate into hernandulcin. An isoxazoline derivative **7** was then made from farnesal oxime.[5] The reaction of (2*Z*,6*E*)-farnesal with hydroxylamine in pyridine afforded a mixture of (*E*)- and (*Z*)-oximes **5a** in a ratio of 4:1. Exposure of the mixture to aqueous sodium hypochlorite in dichloromethane with triethylamine as a catalyst at 0 °C resulted in the formation of a corresponding nitrile oxide (**6**), which was simultaneously cyclized by an intramolecular 1,3-dipolar cycloaddition to give an isoxazoline **7** in 83% yield. By means of the same reactions (2*E*, 6*E*)-farnesal oxime (**5b**) afforded the same isoxazoline **7** in poor yield (28%), besides 55% of nitrile derivative **8**. The stereochemistry of the isoxazoline **7** was assigned from the stereoselectivity of the cycloaddition of nitrile oxide. A catalytic hydrogenation of the isoxazoline in the presence of a deactivated Raney nickel afforded dihydrohernandulcin (**9a**) as a diastereomeric mixture.[6,7] The mixture of dihydro compounds was converted into a phenylseleno compound **10** after protecting the hydroxyl group with trimethyl silyl ether.[8] An oxidative elimination of the selenyl group by hydrogen peroxide[9] gave trimethylsilylhernandulcin in an overall yield 62% from the isoxazoline **7**. Removing the protecting group with dilute hydrogen fluoride[10] yielded hernandulcin (**1**) in quantitative yield.

Experimental

Proton magnetic resonance (^{1}H NMR) spectra were recorded on either a JEOL FX90Q spectrometer or a Bruker AM500 spectrometer with chemical shifts given in parts per million (δ) downfield from tetramethylsilane as an internal standard. Carbon magnetic resonance (^{13}C NMR) spectra were recorded at either 22.5 MHz on a JEOL EX 90 Q or 125 MHz on a Bruker AM 500 instrument. Infrared (IR) spectra were measured on a Hitachi 215 or a JASCO FT/IR-3 spectrophotometer. Mass spectra (MS) were obtained on a Hitachi RMU-6H GC/MS system using electrons of 70 eV ionization energy. Ultraviolet (UV) spectra were recorded on a Hitachi EPS-3T spectrophotometer. Elemental analyses were performed by the University of Tsukuba chemical analysis center. Gas chromatography data were obtained with a 063 Hitachi gas chromatograph by using a 1.7 m/3 mm i.d. glass column packed with 5% SE-30. Wako C-300 silica gel was used for flash column chromatography. Merck Kiesel gel 60 F-254 were used for analytical (0.25 mm) and preparative (0.5 mm) thin-layer chromatography.

(2*Z*,6*E*)-3,7,11-Trimethyl-2,6,10-dodecatrienal Oxime (5a). The (2*Z*,6*E*)-farnesal (2.61 g, 11.9 mmol, prepared by the procedure of Iwashita)[11] was dissolved in 100 ml pyridine and a recrystallized hydroxylamine hydrochloride (1.08 g, 15.5 mmol) was added. The reaction mixture was stirred for 10 min and the resulting mixture was poured into 200 ml of ether, washed with a saturated $CuSO_4$ solution and water, dried (Na_2SO_4), and concentrated to an odorous oil. The residue was purified by flash chromatography (SiO_2, hexane/ethyl acetate 9:1) to give **5a** (2.77 g, 99%). Though initially a mixture of the (*E*)-(80%) and (*Z*)-(20%) oximes, it gradually isomerized to only the (*E*)-form. The physical data of the (*E*)-oxime isomer are as follows: IR($CHCl_3$) 3560, 3250, 2900, 1635, and 1430 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ= 1.60 (6H, s, CH_3×2), 1.68 (3H, s, CH_3), 1.86 (3H, br, s, CH_3), 1.86—2.19 (8H, m, CH_2CH_2, CH_2CH_2), 5.08 (2H, br, t), 5.90 (1H, d, J=10 Hz), 8.00 (1H, d, J=10 Hz), and 8.05 (1H, br, s); ^{13}C NMR ($CDCl_3$) δ=16.1 (q), 17.7 (q), 24.2 (q), 25.7 (q), 26.8 (t), 32.0 (t), 32.8 (t), 39.7 (t), 118.9 (d), 123.0 (d), 124.3 (d), 131.4 (s), 136.4 (s), 147.8 (s), and 148.7 (d); MS m/z (rel intensity %) 235 (M$^+$, 13), 217 (83), 202 (12), 135 (85), 120 (66), 110 (92), and 82 (100). The physical data of (*Z*)-isomer are as follows: ^{1}H NMR ($CDCl_3$) δ=1.60 (6H, s), 1.68 (6H, s), 1.86—2.19 (8H, m), 5.08 (2H, br, t), 6.50 (1H, br, d), and 7.26 (1H, br, d). Found: C, 76.70; H, 10.82; N, 6.01%. Calcd for $C_{15}H_{25}ON$: C, 76.54; H, 10.71; N, 5.95%.

(2*E*,6*E*)-3,7,11-Trimethyl-2,6,10-dodecatrienal Oxime (5b). The (2*E*,6*E*)-farnesal (4.71 g, 21.4 mmol, prepared by a procedure of Iwashita)[11] was dissolved in 150 ml of pyridine and a hydroxylamine hydrochloride(1.93 g, 27.8 mmol) was added. The reaction mixture was stirred for 10 min and then worked up, as described for (2*Z*, 6*E*)-farnesal oxime. Chromatography (SiO_2, hexane/ethyl acetate 8:2) provided a mixture of (*E*)-(80%) and (*Z*)-(20%) oximes (4.93 g, 98%), which gradually isomerized to only the (*E*)-form. The physical data of (*E*)-oxime are as follows: ^{1}H NMR ($CDCl_3$) δ=1.61 (6H, s, CH_3×2), 1.68 (3H, s, CH_3), 1.86 (3H, br, d, CH_3), 1.82—2.15 (8H, m, CH_2CH_2, CH_2CH_2), 5.10 (2H, br, t), 5.93 (1H, d, J=10 Hz), 8.07 (1H, d, J=10 Hz), and 8.42 (1H, br, s); ^{13}C NMR ($CDCl_3$) δ=16.0 (q), 17.2 (q), 17.6 (q), 25.7 (q), 26.3 (t), 26.8 (t), 39.8 (t), 40.1 (t), 118.0 (d), 123.4 (d), 124.4 (d), 130.2 (s), 134.1 (s), 147.7 (s), and 149.1 (d). The data of (*Z*)-oxime are as follows: ^{1}H NMR ($CDCl_3$) δ=1.61 (9H, s, CH_3×3), 1.68 (3H, s, CH_3), 1.82—2.15 (8H, m, CH_2CH_2, CH_2CH_2), 5.10 (2H, br, t), 6.52 (1H, d, J=9.5 Hz), and 7.35 (1H, d, J=9.5 Hz).

3,6-Dimethyl-1,3,3a,4,5,7a-hexahydro-3-(4-methyl-3-pentenyl)-2,1-benzisoxazole (7). To a vigorously stirred solution of the (2*Z*, 6*E*)-farnesal oxime (**5a**) (0.183 g, 0.78 mmol) in 30 ml of dichloromethane cooled to 0 °C was added 1 ml of commercial 11% aqueous sodium hypochlorite dropwise. After 1 h, TLC analysis revealed that the oxime had been consumed; stirring was stopped, the ice bath was removed, and the reaction mixture was allowed to stand overnight. The organic phase was separated and the aqueous phase was extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure. The resulting crude oil was chromatographed (Wakogel C-300, hexane/ethyl acetate 5:1) to provide 0.15 g (83%) of the isoxazoline as an oil. IR (film) 2971, 2929, 2858, 1718, 1650, 1447, 1378, 1110, 894, and 866 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.11 (3H, s), 1.61 (3H, s), 1.67 (3H, s), 1.85 (3H, s), 1.64—2.23 (8H, m), 2.85 (1H, dd, J=4.6, 13 Hz), 5.09 (1H, br, t), and 6.18 (1H, s); ^{13}C NMR ($CDCl_3$) δ=17.7 (q), 19.9 (q), 22.7 (t), 23.2 (t), 23.8 (q), 25.6 (q), 31.3 (t), 39.9 (t), 51.9 (d), 87.4 (s), 114.3 (d), 123.9 (d), 131.9 (s), 158.2 (s), and 158.4 (s); MS m/z 235, 234, 233 (M$^+$), 218, 217, 215, 203, 200, 192, 191, 188, 135, 133 (base), 105, and 101; Found: C, 77.32; H, 9.90; N, 6.09%. Calcd for $C_{15}H_{23}ON$: C, 77.20; H, 9.94; N, 6.00%.

The same reaction was repeated with oxime (**5b**). To a stirred solution of the (2*E*, 6*E*)-farnesal oxime (**5b**) (1.2 g, 5.1 mmol) in dichloromethane (200 ml) was added 11% aqueous sodium hypochlorite (8 ml) dropwise at 0 °C. After 1 h, chromatography of the reaction mixture on a Wakogel C-300 (CH_2Cl_2/CH_3OH 20:1) gave the less polar nitrile (**8**) (0.61 g, 55%) as an oil. IR ($CHCl_3$) 2950, 2900, 2840, 2270, 1615, 1428, 1375, 1344, 1290, and 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.85 (6H, s), 1.67 (3H, s), 1.98 (3H, br, s), 2.00—2.30 (8H, m), 5.05 (2H, br, s), and 5.12 (1H, s); ^{13}C NMR ($CDCl_3$) δ=16.13 (q), 17.76 (q), 20.82 (q), 25.75 (q), 25.81 (t), 26.67 (t), 38.44 (t), 39.69 (t), 95.0 (d), 95.0 (s), 122.4 (d), 124.2 (d), 131.6 (s), 136.8 (s), and 160.6 (s); MS m/z 217 (M$^+$), 202, 175, 148, 146, 123, 122, 121, 108, 107, 106, 93, 91, 80 (base), 69, and 53. The more polar compound (0.33 g, 28%) was identified as same isoxazoline as **7**.

2-(1-Hydroxy-1,5-dimethyl-4-hexenyl)-5-methylcyclohexanone (9a). A mixture of W-2 Raney nickel (0.4 g), which was deactivated prior to use by refluxing for 3 h with acetone, the isoxazoline **7** (0.4 g, 1.72 mmol), an acid solution made from 0.001 mol BCl_3 and 1 ml of methanol, and 100 ml of 5 : 1 $MeOH/H_2O$, was stirred under a hydrogen-filled balloon for 30 min. The reaction mixture was filtered and the filter was washed with MeOH. The combined filtrates were concentrated under reduced pressure. The residue was partitioned between ether and water. The organic phase was dried over Na_2SO_4 and concentrated to afford a crude oil (0.35 g, 85%), which was used without further purification for the next silylation step. An analytical sample was separated by preparative TLC. Spectral data were obtained with a mixture of two diastereomers (**9a**) in a ratio of 55 : 45. IR (film) 3600—3300, 2956, 2928, 2871, 1699, 1458, and 1420 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.02 and 1.20 (totally 3H, d, *J*=7.5 Hz), 1.18 (3H, s), 1.59 (3H, s), 1.67 (3H, s), 1.41—2.30 (11H, m), 2.38 (1H, dd), 3.95 (1H, s), and 5.08 (1H, br, t). ^{13}C NMR ($CDCl_3$) δ=17.7 (q), 22.1 (q), 22.3 (q), 23.8 (q), 25.7 (t), 28.5 (t), 34.1 (t), 35.4 (t), 40.6 (t), 51.6 (d), 56.9 (d), 73.0 (s), 124.6 (d), 131.5 (s), and 215.4 (s); MS *m/z* 238 (M^+), 223, 222, 221, 220 (base), 192, 191, 190, 189, 179, 178, 177, 162, 154, and 138. Found: C, 75.73; H, 10.89%. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00%.

2-(1-Trimethylsilyloxy-1,5-dimethyl-4-hexenyl)-5-methylcyclohexanone (9b). To a mixture of dry triethylamine (0.76 g, 7.56 mmol), crude tertiary alcohol **9a** (1.2 g, 5.04 mmol), 0.1 ml of DMSO and dry ether (40 ml) was added trimethylsilyl chloride (0.65 g, 6 mmol) in 10 min with stirring. After 30 min the reaction mixture was poured into ice water (50 ml). After being washed with water, the ethereal solution was dried over Na_2SO_4 and then concentrated under reduced pressure. The crude product was chromatographed on silica gel with hexane/ether 5 : 1 as eluent to yield 1.31 g (84%) of the title compound as a colorless oily diastereomeric mixture. IR (film) 2957, 2927, 2869, 1703, 1457, 1376, 1250, 1042, 840, and 754 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.10 and 0.11 (totally 9H, s), 0.92, 1.00 (totally 3H, d,*J*=7.5 Hz), 1.24 and 1.32 (totally 3H, s), 1.59 (3H, s), 1.69 (3H, s), 1.40—2.20 (11H, m), 2.28 (1H, m), and 5.08 (1H, br, s); MS *m/z* 295 (M^+—15), 285, 226, 220, 219, 203, 183, 175, 106 (base), 91, 79, and 78; Found: C, 69.84; H, 11.13%. Calcd for $C_{18}H_{34}O_2Si$: C, 69.61; H, 11.04%.

6-(1-Trimethylsilyloxy-1,5-dimethyl-4-hexenyl)-3-methyl-2-(phenylseleno)cyclohexanone (10). To a solution of diisopropylamine (0.043 g, 0.42 mmol) in 5 ml of dry THF, was added 0.35 ml of 1.36 M *n*-BuLi (1M=1mol dm^{-3}) in hexane under an argon atmosphere at −78 °C. After being stirred for 30 min at 0 °C, the LDA solution was chilled to −78 °C; then, a solution of **9b** (0.11 g, 0.35 mmol) in 5 ml of THF was added dropwise and the mixture was stirred for 30 min. A solution of benzeneselenenyl chloride (0.08 g, 0.42 mmol) in 3 ml of THF was added rapidly to the enolate solution. After 1.5 h, the reaction mixture was warmed to 0 °C and poured into a saturated $NaHCO_3$ solution (10 ml) and dichloromethane (20 ml). The organic layer was washed with water and saturated NaCl solution. After solvent removal, chromatography on SiO_2 (benzene) gave 0.127 g (78%) of **10** as a mixture of two diastereomers. ^1H NMR ($CDCl_3$) δ=0.11 and 0.12 (totally 9H, s), 1.15 (3H, d), 1.22 and 1.23 (totally 3H, s), 1.54 (3H, s), 1.58 (3H, s), 1.50—2.35 (10H, m), 3.17—3.80 (1H, m), 5.08 (1H, m), and 7.26—7.49 (5H, m); MS *m/z* 465 (M^+), 463, 450, 448, 376, 375, 373, 327, 326, 325 (base), 323, 310, 268, 252, 239, 226, 184, 165, 156, and 137. Found: C, 61.77; H, 8.40%. Calcd for $C_{24}H_{38}O_2SeSi$: C, 61.91; H, 8.23%.

6-(1-Trimethylsilyloxy-1,5-dimethyl-4-hexenyl)-3-methyl-2-cyclohexen-1-one (11). To a solution of 0.16 g (0.344 mmol) of a seleno compound **10** in 3 ml of dichloromethane containing 0.06 ml of pyridine was gradually added 0.1 g of 30% H_2O_2 and 0.1 ml of water at 0 °C. The reaction mixture was stirred vigorously at 25 °C for an additional 15 min and then poured into 40 ml of dichloromethane and 10 ml of a 20% $NaHCO_3$ solution. The aqueous layer was extrated with dichloromethane and the combined organic layers were washed with a 10% HCl solution, saturated NaCl and dried over Na_2SO_4. The organic phase was concentrated in vacuo to afford a residue, which was chromatographed on Wakogel C-300 (hexane/ether 4.5 : 1) to provide 0.1 g of **11** (95%). ^1H NMR ($CDCl_3$) δ=0.10 (9H, s), 1.47 (3H, s), 1.60 (3H, s), 1.65 (3H, s), 1.88 (3H, s), 1.60—2.50 (9H, m), 5.07 (1H, br, t), and 5.76 (1H, s); IR (film) 2965, 2930, 1652, 1210, 1124 cm^{-1}. Found: C, 70.18; H, 10.44%. Calcd for $C_{18}H_{32}O_2Si$: C, 70.07; H, 10.45%.

6-(1-Hydroxy-1,5-dimethyl-4-hexenyl)-3-methyl-2-cyclohexenone (1) (Hernandulcin). To a solution of acetonitrile (3 ml) containing 5% of 40% aqueous HF was added 0.079 g (0.26 mmol) of the silyl ether **11**. After 15 min dichloromethane and water were added. The organic phase was separated and evaporated to give pure hernandulcin (**1**) 0.061 g (100%). An analytical sample was obtained by chromatography on SiO_2 (hexane/ether 2 : 1). IR (film) 3470, 2969, 2935, 2870, 1650, 1215, 1126 and 1022 cm^{-1}. UV (*c* 0.0399, EtOH) λ_{max} 236 nm (13300); ^1H NMR ($CDCl_3$) δ=1.17 (3H, s), 1.47 (2H, ddd, *J*=8.4, 8.4, and 1.2 Hz), 1.62 (3H, s), 1.675 (1H, m), 1.677 (3H, s), 1.96 (3H, s), 2.02 (1H, m), 2.05 and 2.16 (2H, ddt, *J*=14.6, 7.2, and 8.4 Hz), 2.31 (1H, ddd, *J*=18.5, 5.0, and 2.5 Hz), 2.37 (1H, dm, *J*=13.0 Hz), 2.41 (1H, dd,*J*=14.1 and 14.5 Hz), 5.11 (1H, tm, *J*=7.2 Hz), 5.24 (1H, s), and 5.87 (1H, s); ^{13}C NMR ($CDCl_3$) δ= 17.7, 21.7, 23.7, 24.2, 25.2, 25.8, 31.4, 40.3, 52.3, 74.0, 124.6, 127.7, 131.6, 163.5, and 204.1; MS *m/z* 236 (M^+), 218, 110, 95, and 82 (base).

The authors are grateful to Kuraray Co., Ltd. for the kind provision of (2*E*,6*E*)-farnesol.

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