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A facile synthesis of (6*S*,1′*S*)-(+)-hernandulcin and (6*S*,1′*R*)-(+)-epihernandulcin

Jung Hun Kim, Hyun Jin Lim and Seung Hoon Cheon*

College of Pharmacy and Research Institute of Drug Development, Chonnam National University, 300 Yongbong-Dong, Buk-Gu, Gwangju, 500-757, South Korea

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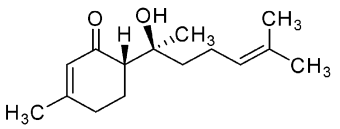
Abstract—A facile total synthesis of (+)-hernandulcin (**1**) was accomplished from (−)-isopulegol in 6 steps with 15% overall yield. Epoxidation of (−)-isopulegol with *m*-chloroperbenzoic acid followed by opening of the epoxide **3a** with prenyl Grignard afforded the tertiary alcohol **4a** with correct C-6 and C-1′ stereochemistry as a major product. Oxidation of the secondary alcohol in compound **4a** to the ketone **5a** was accomplished in high yield by using TPAP and *N*-methylmorpholine *N*-oxide. Conversion of the ketone **5a** to α,β-unsaturated ketone via organoselenium intermediate gave (+)-hernandulcin (**1**). This method was also successfully applied to the synthesis of (+)-epihernandulcin (**2**).

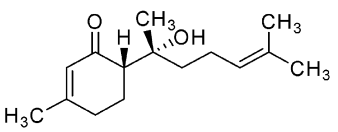
1. Introduction

(+)-Hernandulcin (**1**) was isolated in 1985 by Kinghorn and co-workers[1] as colorless oil from *Lippia dulcis* Trev. (Verbenaceae), obtained at a marketplace near Mexico City. This plant was described in a book entitled Natural History of New Spain that was written between 1570 and 1576 by the Spanish physician Francisco Hernandez. *L. dulcis* is a medicinal plant used by the Aztec people, known to them for centuries by the Nahuatl name '*Tzonpelic xihuitl*', meaning 'sweet herb'.[2] Initially, (+)-hernandulcin was isolated as a minor volatile oil constituent with a very low yield (0.004% w/w). Later the yield was improved to 0.154% (w/w) by isolating from *L. dulcis* leaves and flowers collected in Panama, where it was being sold as a remedy for respiratory ailments.[3] It has been shown that (+)-hernandulcin could be produced from transformed shoot cultures of *L. dulcis* in a yield of 2.9% dry weight.[4] (+)-Hernandulcin was judged, on a molar basis, by human taste panel to be more than three orders of magnitude sweeter than sucrose. Its sweetness, however, was considered somewhat less pleasant than that of sucrose, and some bitterness, off- and after-taste were perceived as well.[5] The tertiary alcohol unit at C-1′ and the C-1 carbonyl group are considered as corresponding to Shallenberger's[6] AH (H-bond donor) and B (H-bond acceptor) units, respectively, since either acetylation of the C-1′ hydroxyl group or reduction of the C-1 carbonyl led to elimination of sweetness. In addition, molecular mechanics calculations revealed that these two functionalities were about 2.6 Å apart in the preferred conformation of hernandulcin, consistent with Shallenberger's model for sweet substances.[7] (±)-Hernandulcin showed no acute toxicity to mice at doses up to 2 g per kilogram of body weight nor mutagenic activity.[3]

The structure of hernandulcin, bisabolane sesquiterpene, was determined by NMR studies and confirmed by total synthesis from 3-methyl-2-cyclohexen-1-one.[1] The absolute stereochemistry of hernandulcin was established by chemical method of synthesizing all four possible stereoisomers from (*R*)- and (*S*)-limonene by Mori and Kato and it was found that only the natural (6*S*,1′*S*)-(+)-hernandulcin possessed sweetness.[8] Although Mori's synthesis provided the natural (+)-hernandulcin in 5 steps, the synthetic method is not considered practical due to 1% overall yield. Racemic hernandulcin has been synthesized by using either boron and silicon enolate,[9] or intramolecular nitrile oxide cycloaddition reaction[10] or titanium chloride catalyzed Diels–Alder reaction.[11] In this paper we wish to report in detail the practical synthesis of (6*S*,1′*S*)-(+)-hernandulcin (**1**) and (6*S*,1′*R*)-(+)-epihernandulcin (**2**) from (−)-isopulegol in 6 steps with 15 and 11% overall yields, respectively.[12]



(6S,1'S)-(+)-Hernandulcin (**1**)



(6S,1'R)-(+)-Epihernandulcin (**2**)

Keywords: hernandulcin; isopulegol; epoxidation; natural sweetener.

* Corresponding author. Tel.: +82-625-302929; fax: +82-625-302911; e-mail: shcheon@chonnam.ac.kr

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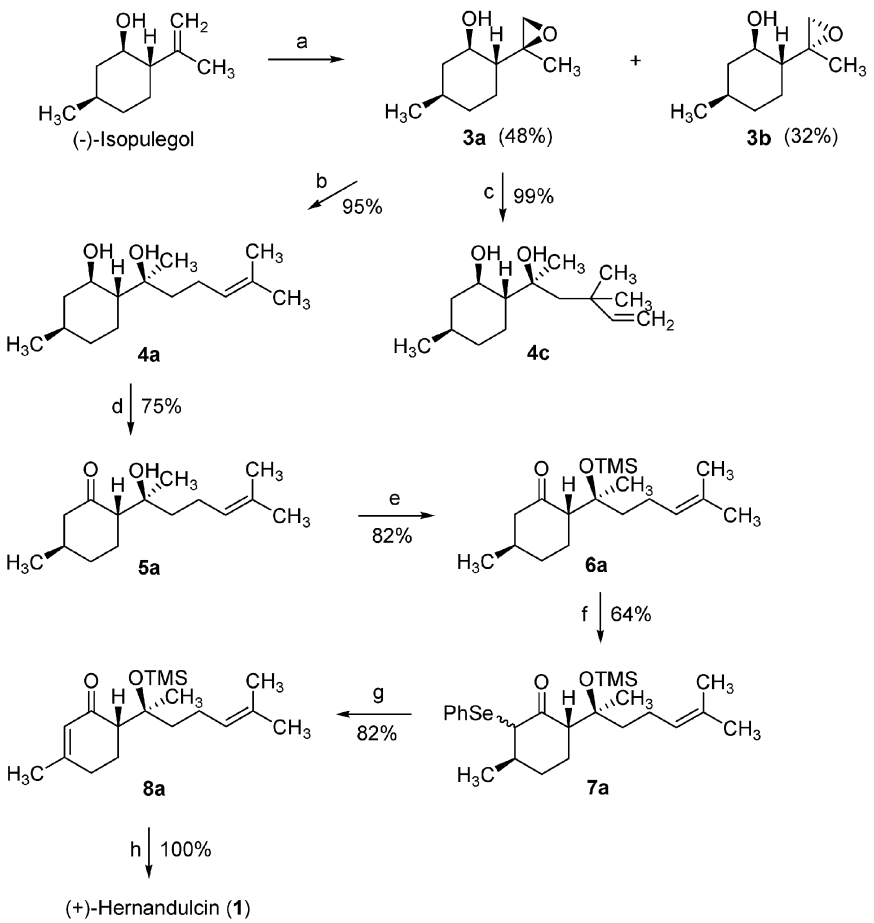
2. Results and discussion

The syntheses commenced with (−)-isopulegol that has the desired C-6 stereochemistry of (6*S*,1′*S*)-(+)-hernandulcin. Homoallylic epoxidation of (−)-isopulegol with *m*-chloroperbenzoic acid in dry methylene chloride at 0°C under Ar furnished the epoxides **3a** and **3b** in 80% yield (Scheme 1). The two epoxides were separated by column chromatography to give a less polar isomer **3a** (48%) and a more polar isomer **3b** (32%). The structures were assigned retrospectively after completion of the synthesis of (+)-hernandulcin.

Attempts to improve the stereoselectivity of homoallylic epoxidation were unsuccessful. Homoallylic epoxidation using *tert*-butyl hydroperoxide[13] in the presence of catalytic amount of $VO(acac)_2$ or $Mo(CO)_6$ gave **3b** as a major product (Table 1). Epoxidation of (−)-isopulegol with NaOCl or MCPBA in methylene chloride in the presence of catalytic amount of Jacobsen reagent[14] gave variable results as shown in Table 1. Interestingly (*R*,*R*)-(−)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino-manganese(III) chloride afforded **3a** as a major product but (*S*,*S*)-(−)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino-manganese(III) chloride yielded variable results depending on oxidants.

Opening of the epoxide **3a** with prenylmagnesium chloride in the presence of purified copper iodide in dry tetrahydrofuran at −30°C under Ar gave **4a** in 95% yield. When this reaction was carried out in the presence of unpurified CuI[15] or without CuI, product **4c** was formed exclusively.[16] The other epoxide **3b** underwent similar reaction to afford **4b** in quantitative yield (Scheme 2). Oxidation of the diol **4a** and **4b** to the β-hydroxyketone **5a** and **5b**, respectively, was carried out in the presence of catalytic amount of tetra-*n*-propylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO) in methylene chloride at room temperature.[17] This mild oxidation reaction furnished the desired β-hydroxyketone **5a** and **5b** in 75 and 78% yield, respectively. Swern oxidation[18] or oxidation with other oxidizing agents such as Dess–Martin periodinane,[19] pyridinium chlorochromate[20] with sodium acetate gave no appreciable amount of product. The tertiary alcohol in **5a** and **5b** was protected to prevent retro-aldol condensation in subsequent reactions by reacting with chlorotrimethylsilane in pyridine at 0°C to afford **6a** and **6b** in 82 and 81% yield, respectively. Conversion of the ketone **6a** to the α,β-unsaturated ketone **8a** was accomplished via the selenide **7a**. Enolization of **6a** with lithium diisopropylamide in tetrahydrofuran at −78°C followed by addition of PhSeCl in the presence of hexamethylphosphoramide at −78°C gave **7a** in 64% yield. An oxidative elimination of



Scheme 1. *Reagents and conditions*: (a) *m*-chloroperbenzoic acid, CH_2Cl_2, 0°C, 3 h; (b) 4-chloro-2-methyl-2-butene, Mg turnings, 1,2-dichloroethane, THF, CuI, −30°C, 1.5 h; (c) 4-chloro-2-methyl-2-butene, Mg turnings, 1,2-dichloroethane, THF, −30°C, 1.5 h; (d) tetra-*n*-propylammonium perruthenate, *N*-methylmorpholine *N*-oxide, molecular sieves (4 Å), CH_2Cl_2, rt, 15 min; (e) TMSCl, pyridine, 0.5 h; (f) LDA, phenylselenenyl chloride, HMPA, THF, −78°C, 2 h; (g) 30% H_2O_2, pyridine, CH_2Cl_2, 0°C, 15 min; (h) 40% HF, CH_3CN, 15 min.

Table 1. Epoxidation of (−)-isopulegol with various oxidants and catalysts

Catalyst	Oxidant	Solvent	Temperature	Ratio of **3a**:**3b**
$VO(acac)_2$	TBHP	Benzene	Reflux	45:55
$Mo(CO)_6$	TBHP	CH_2Cl_2	Reflux	40:60
(*R*,*R*)-Jacobsen reagent[a]	NaOCl	CH_2Cl_2	0°C	60:40
(*S*,*S*)-Jacobsen reagent[b]	NaOCl	CH_2Cl_2	0°C	50:50
(*R*,*R*)-Jacobsen reagent[a]	MCPBA–NMO	CH_2Cl_2	−70°C	60:40
(*S*,*S*)-Jacobsen reagent[b]	MCPBA–NMO	CH_2Cl_2	−70°C	40:60

[a] (*R*,*R*)-(−)-*N*,*N*′-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino-manganese(III) chloride.
[b] (*S*,*S*)-(−)-*N*,*N*′-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino-manganese(III) chloride.

the phenylselenenyl group of **7a** with 30% hydrogen peroxide in methylene chloride containing pyridine gave **8a** in 82% yield. Compound **6b** underwent the similar reactions to provide **8b** in 58% overall yield in two steps.

Finally, removal of the trimethylsilyl protecting group in **8a** and **8b** with 40% HF in acetonitrile afforded (6*S*,1′*S*)-(+)-hernandulcin (**1**) ($[\alpha]_D^{26}$=+110.5° (*c*=0.11, EtOH), lit. $[\alpha]_D^{25}$=+109° (*c*=0.11, EtOH),[1] $[\alpha]_D^{20}$=+122° (*c*=0.111, EtOH),[8a] $[\alpha]_D^{22}$=+126° (*c*=0.113, EtOH)[8b]) and (6*S*,1′*R*)-(+)-epihernandulcin (**2**) ($[\alpha]_D^{27}$=+141.0° (*c*=0.12, EtOH), lit. $[\alpha]_D^{15}$=+141° (*c*=0.111, EtOH)[8b]) in quantitative and 97% yield, respectively. Spectral and analytical data for **1** and **2** were identical with those reported.[1,8b]

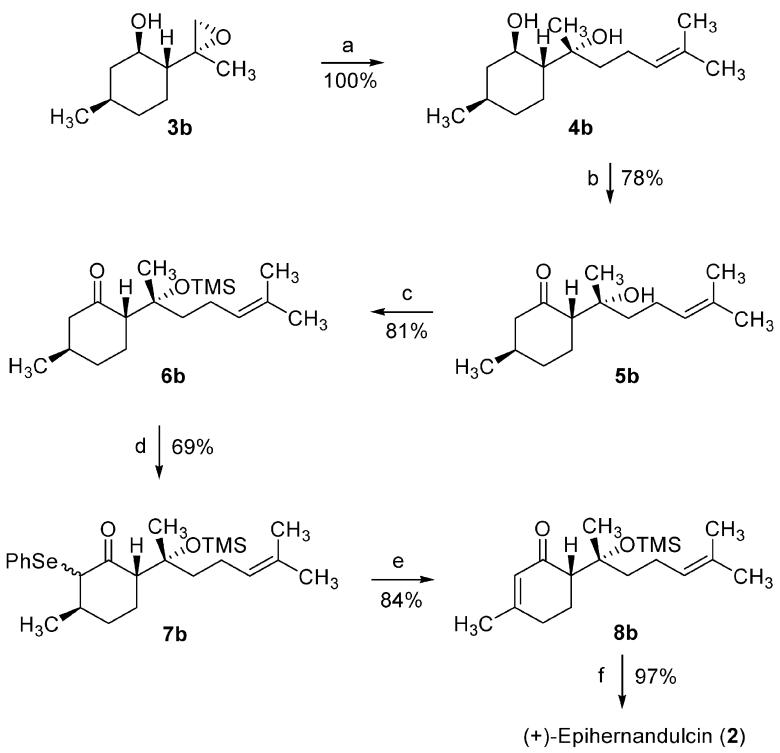
3. Conclusion

In summary, (+)-hernandulcin (**1**) and (+)-epihernandulcin (**2**) were synthesized in 15 and 11% overall yield, respectively, from (−)-isopulegol in 6 steps which represents the most efficient total synthesis of both compounds.

4. Experimental

4.1. General

Reaction mixtures were normally stirred magnetically except the ones vigorous stirring for which mechanical stirrer was used. All nonvolatile samples were pumped to constant weight at room temperature after the removal of solvents under reduced pressure. Unless otherwise noted, most materials were obtained from commercial suppliers and were used without purification. (−)-Isopulegol was purchased from Aldrich (Cat. No. 43,906-1; listed optical rotation is $[\alpha]_D^{20}$=−22° (neat), but measured optical rotation in our laboratories was $[\alpha]_D^{29}$=−20.15° (neat)). 4-Chloro-2-methyl-2-butene was distilled at 109–112°C under argon immediately prior to use. Copper iodide was purified from aqueous potassium iodide.[15] *N*,*N*-Diisopropylamine was distilled under argon from NaOH. Dimethyl sulfoxide (DMSO) was distilled under argon from calcium hydride. HMPA was distilled under argon from sodium metal. CH_2Cl_2 was distilled from phosphorus pentoxide. Tetrahydrofuran (THF) was distilled from sodium and benzophenone



Scheme 2. *Reagents and conditions*: (a) 4-chloro-2-methyl-2-butene, Mg turnings, 1,2-dichloroethane, THF, CuI, −30°C, 1.5 h; (b) tetra-*n*-propylammonium perruthenate, *N*-methylmorpholine *N*-oxide, molecular sieves (4 Å), CH_2Cl_2, rt, 15 min; (c) TMSCl, pyridine, 0.5 h; (d) LDA, phenylselenenyl chloride, HMPA, THF, −78°C, 2 h; (e) 30% H_2O_2, pyridine, CH_2Cl_2, 0°C, 15 min; (f) 40% HF, CH_3CN, 15 min.

immediately prior to use. Thin layer chromatography (TLC) was carried out using Merck Kiesel gel 60 F-254. Column chromatography was performed using Merck 60, 70–230 mesh silica gel. Nuclear magnetic resonance (NMR) data for ^{1}H NMR and ^{13}C NMR were taken on Bruker AC 80 and Varian UNITY plus 300 spectrometers and are reported in δ (ppm) downfield from tetramethylsilane (TMS). The following abbreviations were used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=doublet of doublets, dt=doublet of triplets, ddd=doublet of doublet of doublets. Infrared spectra (IR) were determined in KBr cell on a Jasco FT-IR instrument and were reported in reciprocal centimeters. Optical rotations were measured on a Jasco DIP-1000 polarimeter.

4.1.1. (1*R*,2*R*,5*R*,1′*S*)-5-Methyl-2-(1′-methyl-oxiranyl)-cyclohexanol (3a) and (1*R*,2*R*,5*R*,1′*R*)-5-methyl-2-(1′-methyl-oxiranyl)-cyclohexanol (3b). To a stirred and ice-cooled mixture of (−)-isopulegol ($[\alpha]_D^{29}=-20.15°$ (neat); 2.74 g, 17.7 mmol) in 25.5 mL of dry CH_2Cl_2 was added dropwise 70% *m*-chloroperbenzoic acid (4.56 g, 18.5 mmol) in 70 mL of dry CH_2Cl_2 over 30 min at 0°C under Ar. The mixture was stirred at 0°C for 3 h. Then saturated $NaHCO_3$ solution (40 mL) was added to the mixture. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic solution was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane/EtOAc, 3.5:1) to give the less polar isomer **3a** (1.50 g, 48.2%) and the more polar isomer **3b** (0.96 g, 31.9%).

Compound **3a**, TLC R_f=0.44 (hexane/EtOAc, 1:1); mp 34–35°C; $[\alpha]_D^{30}=-17.9$ (*c*=10, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.71 (dt, *J*=10.5, 4.5 Hz, 1H, H-1), 2.82 (s, 1H, OH), 2.54, 2.59 (each d, *J*=4.8 Hz, 2H, epoxide), 2.08–1.98 (m, 1H), 1.80–1.63 (m, 2H), 1.52–1.36 (m, 1H), 1.31 (s, 3H, 1′-CH_3), 1.27–1.15 (m, 1H), 1.10–0.80 (m, 3H), 0.93 (d, *J*=6.6 Hz, 3H, 5-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 71.2, 59.1, 52.8, 51.2, 43.5, 33.9, 30.9, 27.7, 22.0, 16.9; IR (KBr, cm^{-1}) 3478, 2921, 1454, 1059, 910, 803, 528; HRMS (FAB+) calcd for $C_{10}H_{18}O_2Na$ 193.1204, found 193.1204.

Compound **3b**, TLC R_f=0.38 (hexane/EtOAc, 1:1); mp 54–55°C; $[\alpha]_D^{30}=-16.6$ (*c*=10, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.39–3.23 (m, 2H), 2.66, 2.92 (each d, *J*=4.2 Hz, 2H, epoxide), 1.97–1.83 (m, 2H), 1.73–1.63 (m, 1H), 1.52–1.38 (m, 2H), 1.37 (s, 3H, 1′-CH_3), 1.18–0.83 (m, 3H), 0.93 (d, *J*=6.6 Hz, 3H, 5-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.5, 60.2, 52.2, 49.0, 42.9, 33.9, 31.1, 27.6, 22.0, 20.8; IR (KBr, cm^{-1}) 3410, 2924, 1454, 1030, 859, 811, 605; HRMS (FAB+) calcd for $C_{10}H_{18}O_2Na$ 193.1204, found 193.1204.

4.1.2. (1*R*,2*R*,5*R*,1′*S*)-2-(1′-Hydroxy-1′,5′-dimethyl-4′-hexenyl)-5-methyl-cyclohexanol (4a). Prenyl Grignard reagent was prepared from 4-chloro-2-methyl-2-butene (0.79 mL, 7.02 mmol) and Mg turning (205 mg, 8.42 mmol) in 14 mL of dry THF, employing a catalytic amount of 1,2-dichloroethane as an initiator. To a stirred and cooled mixture of **3a** (200 mg, 1.17 mmol) and CuI (11 mg, 0.059 mmol) in 8 mL of dry THF was added dropwise the prenyl Grignard reagent over 30 min at −30°C under Ar and the resulting mixture was stirred at −30°C for 1.5 h. The reaction mixture was then poured into the mixture of saturated NH_4Cl (10 mL) and 1N HCl solution (10 mL). The organic layer was separated and the aqueous layer was extracted with ether. The combined organic phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane/EtOAc, 4:1) to give **4a** (267 mg, 95%). TLC R_f=0.65 (hexane/EtOAc, 1:1); $[\alpha]_D^{27}=+47.3$ (*c*=0.11, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.13 (m, 1H, H-4′), 3.77 (dt, *J*=10.5, 4.0 Hz, 1H, H-1), 2.54 (s, 2H, OH), 2.22–1.92 (m, 3H), 1.69 (s, 3H, 5′-CH_3), 1.68–1.62 (m, 2H), 1.64 (s, 3H, 5′-CH_3), 1.61–1.52 (m, 1H), 1.50–1.38 (m, 3H), 1.21 (s, 3H, 1′-CH_3), 1.14–0.87 (m, 3H), 0.92 (d, *J*=6.3 Hz, 3H, 5-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.1, 124.4, 76.8, 72.4, 50.6, 44.7, 41.3, 34.6, 31.3, 26.7, 25.7, 23.0, 22.0, 21.3, 17.7; IR (neat, cm^{-1}) 3305, 2922, 1454, 1376, 1192, 1051, 911, 881; HRMS (FAB+) calcd for $C_{15}H_{29}O_2$ 241.2168, found 241.2165.

4.1.3. (1*R*,2*R*,5*R*,1′*R*)-2-(1′-Hydroxy-1′,5′-dimethyl-4′-hexenyl)-5-methyl-cyclohexanol (4b). Prenyl Grignard reagent was prepared from 4-chloro-2-methyl-2-butene (3.53 mL, 31.4 mmol) and Mg turning (916 mg, 37.7 mmol) in 62 mL of dry THF, employing a catalytic amount of 1,2-dichloroethane as an initiator. To a stirred and cooled mixture of **3b** (890 mg, 5.23 mmol) and CuI (50 mg, 0.26 mmol) in 35 mL of dry THF was added dropwise the prenyl Grignard reagent over 30 min at −30°C under Ar and the resulting mixture was stirred at −30°C for 1.5 h. The reaction mixture was then poured into the mixture of saturated NH_4Cl (40 mL) and 1N HCl solution (40 mL). The organic layer was separated and the aqueous layer was extracted with ether. The combined organic phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography (SiO_2, hexane/EtOAc, 4:1) to give **4b** (1.26 g, 100%). TLC R_f=0.71 (hexane/EtOAc, 1:1); $[\alpha]_D^{27}=-20.0$ (*c*=0.11, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.16 (m, 1H, H-4′), 3.79 (dt, *J*=10.5, 4.2 Hz, 1H, H-1), 2.67 (s, 2H, OH), 2.30–2.11 (m, 1H), 2.10–1.90 (m, 2H), 1.73–1.63 (m, 3H), 1.70 (s, 3H, 5′-CH_3), 1.64 (s, 3H, 5′-CH_3), 1.49–1.36 (m, 3H), 1.19 (s, 3H, 1′-CH_3), 1.10–0.85 (m, 3H), 0.91 (d, *J*=6.6 Hz, 3H, 5-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.0, 124.8, 76.7, 72.3, 54.8, 44.9, 35.4, 34.7, 31.4, 26.83, 26.76, 25.7, 22.03, 21.96, 17.7; IR (neat, cm^{-1}) 3305, 2922, 1450, 1376, 1092, 1052, 910, 875; HRMS (FAB+) calcd for $C_{15}H_{29}O_2$ 241.2168, found 241.2164.

4.1.4. (2*S*,5*R*,1′*S*)-2-(1′-Hydroxy-1′,5′-dimethyl-4′-hexenyl)-5-methyl-cyclohexanone (5a). Tetra-*n*-propyl-ammonium perruthenate (TPAP, 7 mg, 0.020 mmol) was added in one portion to a stirred mixture of **4a** (78 mg, 0.32 mmol), *N*-methylmorpholine *N*-oxide (56 mg, 0.48 mmol) and powdered 4 Å molecular sieves (160 mg) in 0.64 mL of dry CH_2Cl_2 at room temperature under Ar. The mixture was stirred at room temperature for 15 min and filtered through a pad of SiO_2, eluting with ethyl acetate. The filtrate was evaporated and the residue was purified by column chromatography (SiO_2, hexane/diethyl ether, 5:1) to give **5a** (57 mg, 75%). TLC R_f=0.67 (hexane/diethyl ether, 1:1); $[\alpha]_D^{25}=-14.0$ (*c*=0.11, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.10 (m, 1H, H-4′), 4.03 (s, 1H, OH), 2.47–2.34 (m, 2H),

2.16–1.80 (m, 6H), 1.69 (d, J=0.9 Hz, 3H, 5′-CH_3), 1.62 (s, 3H, 5′-CH_3), 1.56–1.44 (m, 3H), 1.43–1.32 (m, 1H), 1.19 (s, 3H, 1′-CH_3), 1.03 (d, J=6 Hz, 3H, 5-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.4, 131.4, 124.5, 73.0, 56.7, 51.5, 40.4, 35.3, 33.9, 28.4, 25.7, 23.7, 22.2, 21.9, 17.6; IR (neat, cm^{-1}) 3520, 2954, 1695, 1455, 1375, 1128; HRMS (FAB+) calcd for $C_{15}H_{26}O_2Na$ 261.1830, found 261.1830.

4.1.5. (2*S*,5*R*,1′*R*)-2-(1′-Hydroxy-1′,5′-dimethyl-4′-hexenyl)-5-methyl-cyclohexanone (5b). TPAP (41 mg, 0.12 mmol) was added in one portion to a stirred mixture of **4b** (565 mg, 2.35 mmol), *N*-methylmorpholine *N*-oxide (414 mg, 3.53 mmol) and powdered 4 Å molecular sieves (2.35 g) in 4.7 mL of dry CH_2Cl_2 at room temperature under Ar. The mixture was stirred at room temperature for 15 min and filtered through a pad of SiO_2, eluting with ethyl acetate. The filtrate was evaporated and the residue was purified by column chromatography (SiO_2, hexane/diethyl ether, 5:1) to give **5b** (437 mg, 78%). TLC R_f=0.53 (hexane/diethyl ether, 1:1); $[\alpha]_D^{26}$=−24.7 (c=0.11, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.11 (m, 1H, H-4′), 3.76 (s, 1H, OH), 2.42–2.32 (m, 2H), 2.20–1.80 (m, 6H), 1.68 (d, J=1.2 Hz, 3H, 5′-CH_3), 1.66–1.49 (m, 2H), 1.62 (s, 3H, 5′-CH_3), 1.48–1.31 (m, 2H), 1.22 (s, 3H, 1′-CH_3), 1.02 (d, J=6.3 Hz, 3H, 5-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.0, 131.5, 124.5, 73.0, 58.5, 51.7, 37.9, 35.7, 34.1, 28.1, 25.6, 25.2, 22.2, 22.0, 17.6; IR (neat, cm^{-1}) 3511, 2926, 1697, 1455, 1376, 1121; HRMS (FAB+) calcd for $C_{15}H_{26}O_2Na$ 261.1830, found 261.1834.

4.1.6. (2*S*,5*R*,1′*S*)-2-(1′,5′-Dimethyl-1′-trimethylsilyloxy-4′-hexenyl)-5-methyl-cyclohexanone (6a). To a mixture of **5a** (200 mg, 0.84 mmol) in 8.4 mL of dry pyridine was added dropwise chlorotrimethylsilane (0.43 mL, 3.36 mmol) over 5 min at room temperature under Ar. The mixture was stirred for 30 min at room temperature and water was added to the mixture. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic solution was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane/diethyl ether, 5:1) to give **6a** (214 mg, 82%). TLC R_f=0.53 (hexane/diethyl ether, 5:1); $[\alpha]_D^{26}$=−16.3 (c=0.12, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.12 (m, 1H, H-4′), 2.40 (ddd, J=15.6, 5.1, 0.9 Hz, 1H), 2.35–2.28 (m, 1H), 2.26–2.17 (m, 1H), 2.06–1.80 (m, 5H), 1.75–1.64 (m, 1H), 1.68 (s, 3H, 5′-CH_3), 1.62 (s, 3H, 5′-CH_3), 1.53 (dd, J=12.9, 3.3 Hz, 1H), 1.48–1.38 (m, 1H), 1.37 (s, 3H, 1′-CH_3), 1.32–1.22 (m, 1H), 1.01 (d, J=6.3 Hz, 3H, 5-CH_3), 0.10 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.8, 130.9, 125.0, 76.4, 60.5, 52.0, 38.4, 35.9, 34.3, 27.7, 25.7, 22.34, 22.25, 17.6, 2.6; IR (neat, cm^{-1}) 2956, 1713, 1455, 1374, 1249, 1043, 839, 752; HRMS (FAB+) calcd for $C_{18}H_{35}O_2Si$ 311.2406, found 311.2404.

4.1.7. (2*S*,5*R*,1′*R*)-2-(1′,5′-Dimethyl-1′-trimethylsilyloxy-4′-hexenyl)-5-methyl-cyclohexanone (6b). To a mixture of **5b** (363 mg, 1.52 mmol) in 15 mL of dry pyridine was added dropwise chlorotrimethylsilane (0.77 mL, 6.08 mmol) over 5 min at room temperature under Ar. The mixture was stirred for 30 min at room temperature and water was added to the mixture. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic solution was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane/diethyl ether, 5:1) to give **6b** (382 mg, 81%). TLC R_f=0.58 (hexane/diethyl ether, 5:1); $[\alpha]_D^{26}$=−43.7 (c=0.12, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.04 (m, 1H, H-4′), 2.40 (dd, J=12.3, 4.8 Hz, 1H), 2.32–2.22 (m, 2H), 2.04–1.78 (m, 6H), 1.66 (s, 3H, 5′-CH_3), 1.58 (s, 3H, 5′-CH_3), 1.55–1.31 (m, 3H), 1.29 (s, 3H, 1′-CH_3), 1.01 (d, J=6.0 Hz, 3H, 5-CH_3), 0.10 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.5, 130.9, 124.8, 57.4, 51.9, 40.9, 36.4, 34.4, 27.9, 25.7, 24.2, 22.3, 17.6, 2.6; IR (neat, cm^{-1}) 2956, 1711, 1455, 1373, 1250, 1038, 839, 753; HRMS (FAB+) calcd for $C_{18}H_{35}O_2Si$ 311.2406, found 311.2404.

4.1.8. (3*R*,6*S*,1′*S*)-6-(1′,5′-Dimethyl-1′-trimethylsilyloxy-4′-hexenyl)-3-methyl-2-(phenylseleno)cyclohexanone (7a). To a stirred and cooled solution of *N*,*N*-diisopropylamine (0.10 mL, 0.70 mmol) in 1.5 mL of dry THF, was added 1.6 M *n*-BuLi in hexane (0.37 mL, 0.58 mmol) at −78°C under Ar and the mixture was stirred for 30 min at 0°C. To the above LDA solution was added dropwise a solution of **6a** (100 mg, 0.32 mmol) in 2.9 mL of dry THF at −78°C under Ar and the mixture was stirred for 30 min at −78°C. To this reaction mixture was added rapidly a solution of phenylselenenyl chloride (84 mg, 0.44 mmol) and hexamethylphosphoramide (0.08 mL, 0.44 mmol) in 2.9 mL of dry THF and the mixture was stirred for 1.5 h at −78°C. The reaction mixture was warmed to 0°C and poured into a saturated $NaHCO_3$ solution (10 mL) and CH_2Cl_2. The organic layer was washed water and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, benzene) to give **7a** (95 mg, 64%). TLC R_f=0.53 (hexane/diethyl ether, 5:1); $[\alpha]_D^{26}$=+8.3 (c=0.12, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56–7.20 (m, 5H, C_6H_5), 5.09 (m, 1H, H-4′), 3.80–3.22 (m, 2H), 2.24–1.95 (m, 4H), 1.82–1.30 (m, 5H), 1.66 (d, J=0.9 Hz, 3H, 5′-CH_3), 1.60 (s, 3H, 5′-CH_3), 1.24 (s, 3H, 1′-CH_3), 1.17 (d, J=6.6 Hz, 3H, 3-CH_3), 0.10 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.7, 134.4, 130.9, 129.1, 128.9, 127.8, 125.1, 76.4, 62.0, 55.5, 38.7, 38.2, 30.7, 27.0, 25.7, 25.5, 22.4, 19.8, 17.6, 2.6; IR (neat, cm^{-1}) 2959, 1702, 1249, 1040, 839, 739.

4.1.9. (3*R*,6*S*,1′*R*)-6-(1′,5′-Dimethyl-1′-trimethylsilyloxy-4′-hexenyl)-3-methyl-2-(phenylseleno)cyclohexanone (7b). To a stirred and cooled solution of *N*,*N*-diisopropylamine (0.10 mL, 0.72 mmol) in 1.5 mL of dry THF, was added 1.6 M *n*-BuLi in hexane (0.38 mL, 0.60 mmol) at −78°C under Ar and the mixture was stirred for 30 min at 0°C. To the above LDA solution was added dropwise a solution of **6b** (105 mg, 0.34 mmol) in 3 mL of dry THF at −78°C under Ar and the mixture was stirred for 30 min at −78°C. To the reaction mixture was added rapidly a solution of phenylselenenyl chloride (86 mg, 0.45 mmol) and hexamethylphosphoramide (0.08 mL, 0.45 mmol) in 3 mL of dry THF and the mixture was stirred for 1.5 h at −78°C. Then the reaction mixture was warmed to 0°C and poured into a saturated $NaHCO_3$ solution (10 mL) and CH_2Cl_2. The organic layer was washed water and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, benzene) to give **7b** (109 mg, 69%). TLC R_f=0.58 (hexane/diethyl

ether, 5:1); $[\alpha]_D^{27}=-66.7$ (c=0.12, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58–7.16 (m, 5H, C_6H_5), 4.99 (m, 1H, H-4′), 3.69 (d, J=11.7 Hz, 1H, H-2), 2.69–2.61 (m, 1H), 2.30–2.22 (m, 1H) 2.04–1.86 (m, 4H), 1.78–1.38 (m, 4H), 1.65 (s, 3H, 5′-CH_3), 1.55 (s, 3H, 5′-CH_3), 1.33 (s, 3H, 1′-CH_3), 1.16 (d, J=6.3 Hz, 3H, 3-CH_3), 0.10 (s, 9H, Si$(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.7, 134.2, 131.1, 130.0, 128.9, 127.2, 124.5, 64.9, 58.1, 43.7, 40.6, 35.3, 28.1, 25.7, 24.4, 22.7, 22.3, 17.6, 2.6; IR (neat, cm^{-1}) 2956, 1713, 1249, 1032, 839, 740.

4.1.10. (6*S*,1′*S*)-6-(1′,5′-Dimethyl-1′-trimethylsilyloxy-4′-hexenyl)-3-methyl-2-cyclohexenone (8a). To a solution of **7a** (410 mg, 0.88 mmol) in 9 mL of CH_2Cl_2 containing 0.18 mL of pyridine was gradually added 0.3 g of 30% H_2O_2 and 0.3 mL of water at 0°C. The mixture was stirred vigorously for 15 min at room temperature. It was then poured into CH_2Cl_2 (80 mL) and 20% $NaHCO_3$ solution (40 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane/diethyl ether, 5:1) to give **8a** (223 mg, 82%). TLC R_f=0.32 (hexane/diethyl ether, 5:1); $[\alpha]_D^{27}=+9.7$ (c=0.14, EtOH); ^{1}H NMR (300 MHz, C_6D_6) δ 5.84 (s, 1H, H-2), 5.30 (m, 1H, H-4′), 2.40–1.84 (m, 6H), 1.79–1.60 (m, 2H), 1.67 (s, 6H, 5′-CH_3), 1.57 (s, 3H, 3-CH_3), 1.39 (s, 3H, 1′-CH_3), 0.92–0.76 (m, 1H), 0.15 (s, 9H, Si$(CH_3)_3$); 13C NMR (75 MHz, C_6D_6) δ 198.3, 158.9, 131.0, 128.6, 125.5, 78.1, 55.3, 40.0, 31.0, 27.6, 25.8, 24.4, 23.7, 23.3, 17.7, 2.7; IR (neat, cm^{-1}) 2962, 1668, 1250, 1075, 839, 753; HRMS (FAB+) calcd for $C_{18}H_{33}O_2Si$ 309.2250, found 309.2251.

4.1.11. (6*S*,1′*R*)-6-(1′,5′-Dimethyl-1′-trimethylsilyloxy-4′-hexenyl)-3-methyl-2-cyclohexenone (8b). To a solution of **7b** (100 mg, 0.21 mmol) in 3 mL of CH_2Cl_2 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 mixture was stirred vigorously for 15 min at room temperature. It was then poured into CH_2Cl_2 (20 mL) and 20% $NaHCO_3$ solution (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane/diethyl ether, 5:1) to give **8b** (69 mg, 84%). TLC R_f=0.26 (hexane/diethyl ether, 5:1); $[\alpha]_D^{27}=-12.7$ (c=0.11, EtOH); ^{1}H NMR (300 MHz, C_6D_6) δ 5.84 (s, 1H, H-2), 5.30 (m, 1H, H-4′), 2.49–2.37 (m, 2H), 2.24–2.03 (m, 3H), 1.97–1.70 (m, 3H), 1.69 (s, 3H, 5′-CH_3), 1.65 (s, 3H, 5′-CH_3), 1.39 (s, 3H, 3-CH_3), 1.38 (s, 3H, 1′-CH_3), 0.92–0.76 (m, 1H), 0.15 (s, 9H, Si$(CH_3)_3$); ^{13}C NMR (75 MHz, C_6D_6) δ 198.6, 159.2, 131.1, 125.2, 78.0, 52.6, 43.0, 31.0, 25.8, 25.0, 24.4, 23.3, 23.2, 17.7, 2.7; IR (neat, cm^{-1}) 2963, 1658, 1265, 1040, 840, 740; HRMS (FAB+) calcd for $C_{18}H_{33}O_2Si$ 309.2250, found 309.2253.

4.1.12. (6*S*,1′*S*)-6-(1′-Hydroxy-1′,5′-dimethyl-4′-hexenyl)-3-methyl-2-cyclohexenone ((+)-hernandulcin). To a mixture of acetonitrile (4 mL) and 40% aqueous HF (0.2 mL) was added **8a** (146 mg, 0.47 mmol). The mixture was stirred for 15 min at room temperature. It was then poured into CH_2Cl_2 and water. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic solution was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane/diethyl ether, 2.5:1) to give (+)-hernandulcin (111 mg, 100%). TLC R_f=0.47 (hexane/diethyl ether, 1:1); $[\alpha]_D^{26}=+110.5°$ (c=0.11, EtOH), lit. $[\alpha]_D^{25}=+109°$ (c=0.11, EtOH),[1] $[\alpha]_D^{20}=+122°$ (c=0.111, EtOH),[8a] $[\alpha]_D^{22}=+126°$ (c=0.113, EtOH);[8b] ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (s, 1H, H-2), 5.27 (s, 1H, OH), 5.12 (m, 1H, H-4′), 2.46–2.31 (m, 3H), 2.30–1.98 (m, 3H), 1.97 (s, 3H, 3-CH_3), 1.76–1.64 (m, 1H), 1.69 (d, J=1.2 Hz, 3H, 5′-CH_3), 1.63 (s, 3H, 5′-CH_3), 1.44–1.51 (m, 2H, 2′-CH_2), 1.18 (s, 3H, 1′-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.1, 163.5, 131.5, 127.5, 124.5, 73.9, 52.1, 40.2, 31.3, 25.7, 25.1, 24.1, 23.6, 21.5, 17.6; IR (neat, cm^{-1}) 3454, 2970, 1649, 1381, 1215, 1124, 585; HRMS (FAB+) calcd for $C_{15}H_{25}O_2$ 2371855, found 237.1856.

4.1.13. (6*S*,1′*R*)-6-(1′-Hydroxy-1′,5′-dimethyl-4′-hexenyl)-3-methyl-2-cyclohexenone ((+)-epihernandulcin). To a mixture of acetonitrile (3 mL) and 40% aqueous HF (0.15 mL) was added **8b** (100 mg, 0.32 mmol). The mixture was stirred for 15 min at room temperature. It was then poured into CH_2Cl_2 and water. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic solution was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane/diethyl ether, 2.5:1) to give (+)-epihernandulcin (74 mg, 97%). TLC R_f=0.25 (hexane/diethyl ether, 1:1); $[\alpha]_D^{27}=+141.0°$ (c=0.12, EtOH), lit. $[\alpha]_D^{15}=+141°$ (c=0.111, EtOH);[8b] ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 (s, 1H, H-2), 5.14–5.00 (m, 2H), 2.40–2.31 (m, 3H), 2.29–2.13 (m, 1H), 2.10–2.00 (m, 2H), 1.96 (s, 3H, 3-CH_3), 1.84–1.68 (m, 1H), 1.66 (d, J=1.2 Hz, 3H, 5′-CH_3), 1.61 (s, 3H, 5′-CH_3), 1.55 (dd, J=12, 4.8 Hz, 1H), 1.39 (ddd, J=13.8, 12, 5.4 Hz, 1H), 1.20 (s, 3H, 1′-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.5, 163.4, 131.4, 127.5, 124.7, 74.4, 55.4, 37.0, 31.5, 25.7, 25.4, 25.0, 24.1, 22.1, 17.6; IR (neat, cm^{-1}) 3444, 2972, 1644, 1381, 1265, 1216, 739; HRMS (FAB+) calcd for $C_{15}H_{25}O_2$ 2371855, found 237.1855.

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