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Synthesis of (+)-hernandulcin and (+)-epihernandulcin

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Abstract—(+)-Hernandulcin **1**, an extremely sweet bisabolane-type sesquiterpene, and (+)-epihernandulcin **2** were synthesized in six steps from (−)-isopulegol with 15 and 11% overall yields, respectively.

(+)-Hernandulcin **1** was isolated from *Lippia dulcis* Trev. (Verbenaceae) by Kinghorn and his co-workers in 1985.[1] The structure of hernandulcin was determined by NMR studies[1] and the absolute stereochemistry was established by chemical method of synthesizing all four possible stereoisomers from (*R*)- and (*S*)-limonene by Mori and Kato.[2] It was found that only (6*S*,1′*S*)-(+)-hernandulcin possesses sweetness.[2] (+)-Hernandulcin is 1500 times sweeter than sucrose on a weight basis, although its sweetness was considered somewhat less pleasant than that of sucrose, and some bitterness, off-taste and after-taste were perceived as well.[3] The synthesis of racemic hernandulcin has been reported[4] but the synthesis of (6*S*,1′*S*)-(+)-hernandulcin has not been published except the one reported by Mori and Kato.[2] In this paper we wish to disclose some results culminating in the total synthesis of (6*S*,1′*S*)-(+)-hernandulcin **1** and (6*S*,1′*R*)-(+)-epihernandulcin **2**.

Epoxidation of (−)-isopulegol **3** with *m*-chloroperbenzoic acid in dry CH_2Cl_2 at 0°C under Ar furnished a mixture of two diastereomers which were separated by column chromatography (hexane: ethyl acetate = 7:2) to give a less polar **4** ($[\alpha]_D^{30}$ −17.9° (*c* = 10, ethyl acetate), 48% yield) and a more polar isomer **5** ($[\alpha]_D^{30}$ −16.6° (*c* = 10, ethyl acetate), 32% yield).[5] A number of attempts were made to improve the stereoselectivity of the homoallylic epoxidation but none gave better results. Opening of the epoxide **4** with prenylmagnesium chloride (freshly prepared from prenyl chloride and an excess of Mg in THF) in the presence of purified[6] copper(I) iodide (0.05 equiv.) in dry THF at −30°C under Ar gave **6** ($[\alpha]_D^{27}$ +47.3° (*c* = 0.11, EtOH)) in 95% yield. Opening of the epoxide **4** with prenylmagnesium chloride in the absence of CuI gave **7** in quantitative yield. Oxidation of the secondary alcohol in **6** to the ketone **8** ($[\alpha]_D^{25}$ −14.0° (*c* = 0.11, EtOH)) was carried out in the presence of tetra-*n*-propylammonium perruthenate (TPAP, 0.06 equiv.), and *N*-methylmorpholine *N*-oxide (1.5 equiv.) in CH_2Cl_2 with 75% yield. Either Swern[7] oxidation or Dess–Martin[8] periodinane oxidation gave variable results. Protection of the tertiary alcohol in **8** with chlorotrimethylsilane (3 equiv.) in pyridine afforded **9** ($[\alpha]_D^{26}$ −16.3° (*c* = 0.12, EtOH)) in 82% yield. Treatment of **9** with LDA (1 equiv.), phenylselenyl chloride (1.3 equiv.) and HMPA (1.3 equiv.) in THF at −78°C afforded selenide **10** (64%) which was subjected to an oxidative elimination with 30% H_2O_2 in CH_2Cl_2 containing pyridine to afford **11** ($[\alpha]_D^{27}$ +9.7° (*c* = 0.14, EtOH)) in 82% yield. Finally deprotection of the trimethylsilyl group with 40% HF in CH_3CN gave (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),[2a] $[\alpha]_D^{22}$ +126° (*c* = 0.113, EtOH)[2b]) in quantitative yield. Following the same sequences of reactions as described above (6*S*,1′*R*)-(+)-epihernandulcin **2** ($[\alpha]_D^{27}$ +141.0° (*c* = 0.12, EtOH), lit. $[\alpha]_D^{15}$ +141° (*c* = 0.111, EtOH))[2b,9] was also synthesized starting from the epoxide **5** (Scheme 1).

In conclusion, we have completed an enantiospecific total synthesis of (+)-hernandulcin **1** and (+)-epihernandulcin **2** in six steps from (−)-isopulegol with 15 and 11% overall yields, respectively.

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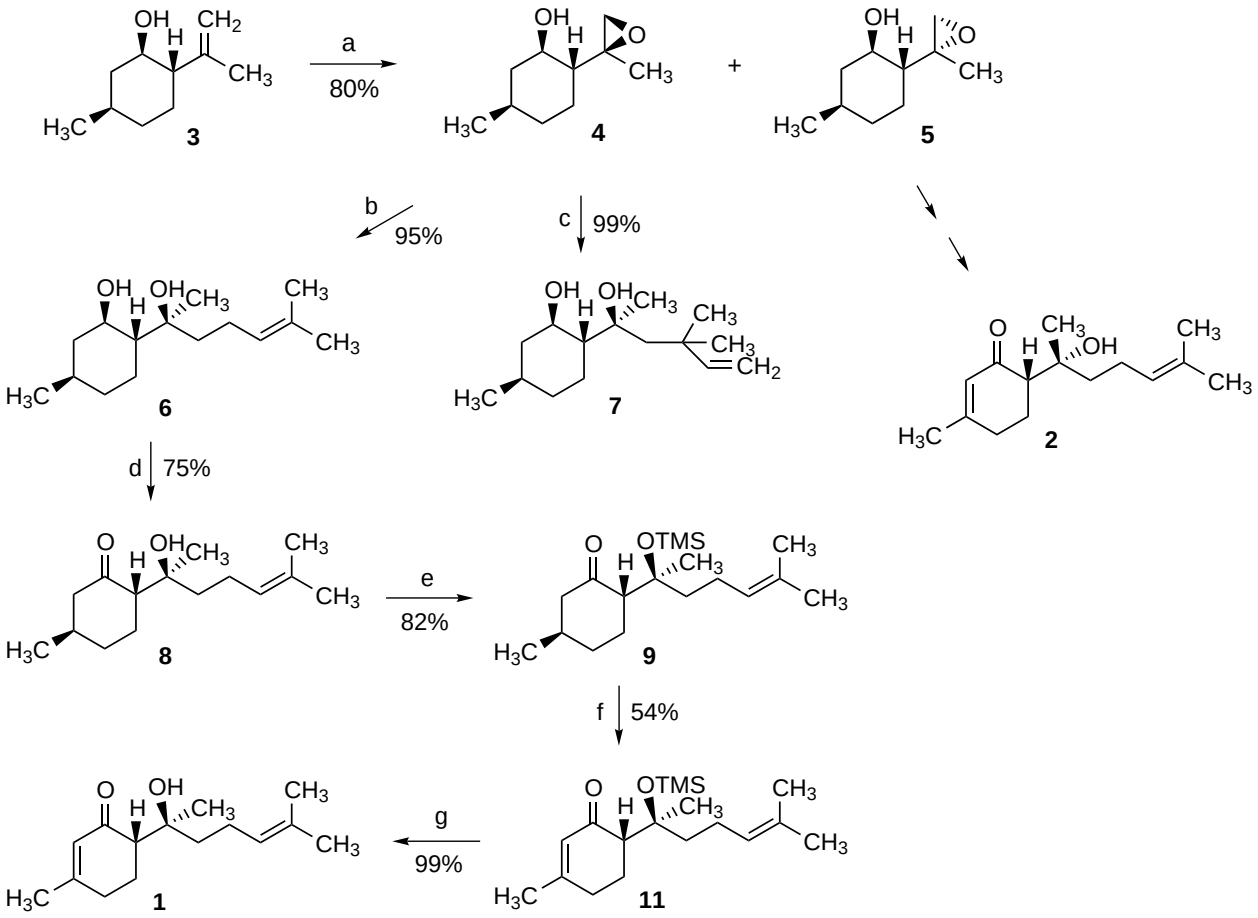

Scheme 1. *Reagents and conditions*: (a) *m*-chloroperbenzoic acid, CH_2Cl_2, 0°C, 3 h; (b) 4-chloro-2-methyl-2-butene, Mg turnings, 1,2-dichloromethane, THF, CuI, −30°C, 1.5 h; (c) 4-chloro-2-methyl-2-butene, Mg turnings, 1,2-dichloromethane, THF, −30°C, 1.5 h; (d) tetra-*n*-propylammonium perruthenate,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

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5. The stereochemistry assigned to **4** and **5** was verified by their conversion to **1** and **2**, respectively.
6. Copper(I) iodide was purified by dissolving 13.2 g of CuI in boiling saturated aqueous KI (130 g) in H_2O (100 mL) over 30 min. followed by cooling, filtering and drying in vacuo for 24 h.
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9. Satisfactory analytical and spectroscopic data have been obtained for all new compounds reported herein.