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Enantiospecific synthesis of (+)-hernandulcin

Francesco G. Gatti *

Dipartimento di Chimica dei Materiali ed Ingegneria Chimica 'G. Natta' del Politecnico, Via Mancinelli 7, 20131 Milano, Italy

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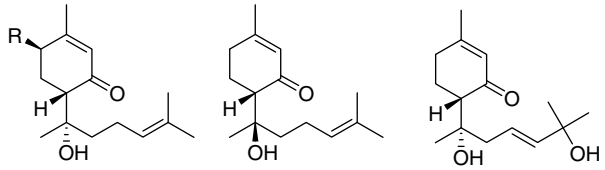
ABSTRACT

The sesquiterpene (+)-hernandulcin has been enantiospecifically synthesized starting from (−)-neoisopulegol in seven steps and in 25% overall yield.

The consumption of sucrose-free foods in the United States is drastically increased over the last decades. Among all artificial sweeteners or so called sugar substitutes, aspartame, saccharin, and cyclamate are without doubt the most popular and employed in the food industry. However, questions regarding the safety of these sweeteners, renewed by a recent study promoted by the Californian Environmental Protection Agency, concluded that an increase in the number of people with brain tumor might be associated with the use of these substances. Thus, the discovery of new sugar substitutes gained interest in the scientific community.[1] In the 1985, Kinghorn et al. isolated, from the leaves and flowers of the tropical American plant *Lippia dulcis* (Verbenaceae), the substance **1**, which, they called (+)-hernandulcin in honor of the Spanish physician Hernández who first described the sweet property of this herb.[2] This compound represents a breakthrough in the field of natural sugar substitutes, since it has been the first bisabolene sesquiterpene that resulted intensively sweet. In contrast, the natural occurring epihernandulcin **2** resulted bitter. The bisabolenes (+)-4β-hydroxy hernandulcin **3** and lippidulcine A **4** have been successively isolated from the same herb.[3,4]

The stereochemistry of **1** has been unambiguously assigned from Mori et al. by total synthesis starting from (+)-limonene and in 1% overall yield.[5] Attempts to synthesize derivatives of **1**, with similar taste properties, showed that the C(1) carbonyl group, the tertiary hydroxyl group and the two double bonds are crucial structural elements for the perception of its sweet taste.[6] Moreover, Mori has shown that only the (6*S*,2′*S*)-**1** enantiomer is sweet.[5]

Recently, Cheon et al. described a new synthesis of **1** starting from the commercially available (−)-isopulegol, improving the overall yield up to 15%.[7] However, this synthesis suffers from two main drawbacks: (i) it is not enantiospecific and (ii) it makes use of the highly toxic selenium chemistry and the harmful hexamethylphosporamide (HMPA) in the last step.



1, R= H
3, R=OH

2

4

Keeping this in mind we disclosed the first enantiospecific synthesis of **1** starting from (+)-neoisopulegol.

Indeed, both reported synthesis introduce the stereocentre at C(2′) carbon by epoxidation, with *m*-chloroperbenzoic acid (MCPBA), of the double bond of (+)-limonene and (−)-isopulegol, respectively. However, both reactions give a mixture of the corresponding epoxides with modest selectivity, and, then require column chromatographic separation of the diastereoisomers. In contrast, it is known from literature that the epoxidation of (+)-neoisopulegol is highly selective.[8] Thus, we envisaged in the (+)-neoisopulegol the most appropriate building block for the preparation of **1**. The (+)-neoisopulegol can be easily prepared from the (−)-isopulegol[9] in two steps (72% overall yield).[8a]

The synthesis of **1** is summarized in Scheme 1. Metalation of (+)-neoisopulegol with butyllithium (2.2 equiv) and potassium-*tert*-butoxide (1.0 equiv) in hexane at 0 °C followed by addition

* Tel.: +39 02 23993072; fax: +39 02 23993080.
E-mail address: Francesco.Gatti@polimi.it.

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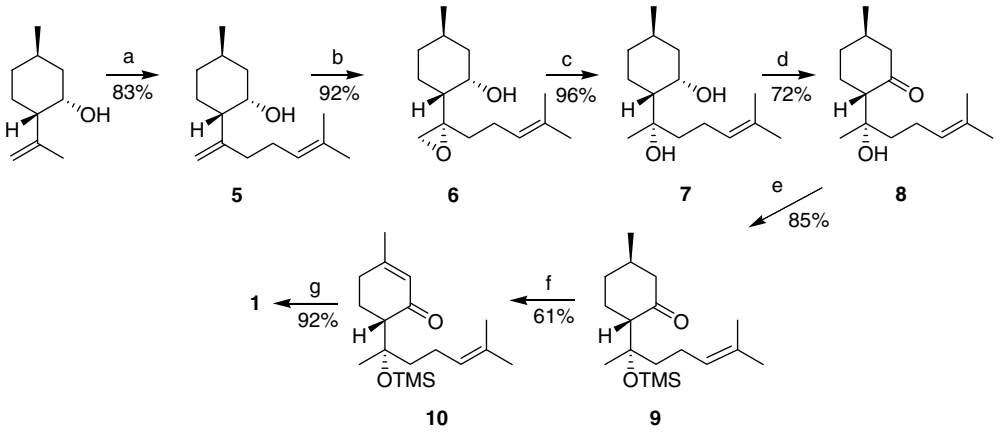

Scheme 1. Reagents and conditions: (a) (i) BuLi, *t*-BuOK, hexane, 0 °C; 4 h; (ii) $BrCH_2CH{=}C(CH_3)_2$; −10 °C, 1 h; (b) TBHP, cat. VO(acac), benzene, rt, 12 h; (c) $LiAlH_4$, THF, 0°C, 1 h; (d) DMP, CH_2Cl_2; rt, 4 h; (e) TMSCl, CH_2Cl_2/pyridine (2:1), 0.5 h; (f) (i) LDA, TMSCl, −78 °C, THF; (ii) DMSO, cat. $Pd(OAc)_2$, 50 °C, O_2, 36 h; (g) TBAF, CH_3CN, 0.5 h.

of prenylbromide (3-methyl-2-butenylbromide) at −10 °C gave dienol **5** ($[\alpha]_D^{25}$ +19.6 (*c* 3.7, $CHCl_3$)) in 83% yield.[10] Epoxidation of the latter with *tert*-butylhydroperoxide (TBHP) in the presence of a catalytic amount of $VO(acac)_2$ in benzene at room temperature gave exclusively the diastereoisomer **6** ($[\alpha]_D^{25}$ +36.6, *c* 3.0, $CHCl_3$) in 92% yield.[8,11] Then, **6** was reduced with $LiAlH_4$ in THF at 0 °C to give the diol **7** in almost quantitative yield as a white solid. The latter was oxidized with Dess-Martin periodinane (DMP)[12] in CH_2Cl_2 at room temperature to give ketone **8** ($[\alpha]_D^{25}$ −10.0 (*c* 1.2, $CHCl_3$), $[\alpha]_D^{25}$ −9.2 (*c* 1.0, EtOH), lit. $[\alpha]_D^{25}$ −14.0 (*c* 0.11, EtOH)[7]) in 72% yield.

Finally, we investigated a new way to convert ketone **8** to enone **1** avoiding the highly toxic selenium chemistry adopted by Cheon. First, we tried the iperiodine chemistry, recently developed by Nicolaou et al. Direct oxidation of **8** to give **1** with *o*-iodoxybenzoic acid (IBX) at high temperature (80 °C) in DMSO failed, indeed, after 12 h all the starting material was recovered.[13] A more efficient evolution of this new methodology consists in the oxidation of the silyl enol ethers by using IBX·N-oxide complexes to give the α,β-unsaturated ketones under milder conditions (room temperature) and in better yields.[14] First, the tertiary hydroxyl group of ketone **8** was protected with chlorotrimethylsilane (TMSCl) in CH_2Cl_2/pyridine (2:1) to give **9** ($[\alpha]_D^{25}$ −11.2 (*c* 1.2, $CHCl_3$), $[\alpha]_D^{25}$ −14.3 (*c* 1.3, EtOH), lit. $[\alpha]_D^{26}$ −16.3 (*c* 0.12, EtOH)[7]) in 85% yield. Then, the kinetic silyl enol ether was generated by treatment of **9** with lithium *di*-isopropylamide (LDA) and TMSCl at −78 °C in THF, and, after standard work-up, was directly submitted to the oxidation step without any further purification.

However, treatment of the latter with IBX and 4-methoxy-pyridine-N-oxide (MPO) in DMSO at room temperature gave just trace of enone **10**. In contrast, the oxidation of the silyl enol ether, using the method of Saegusa–Larock,[15] with a catalytic amount of $Pd(OAc)_2$ (30%, in weight) in DMSO at 50 °C under an oxygen atmosphere, gave enone **10** ($[\alpha]_D^{25}$ +7.8 (*c* 1.1, $CHCl_3$), $[\alpha]_D^{25}$ +9.0 (*c* 1.2, EtOH), lit. $[\alpha]_D^{27}$ +9.7 (*c* 0.14, EtOH)[7]) in 61% yield (over the two steps).

Finally, the cleavage of the silyl protective group was accomplished by treatment of **10** with tetra-*n*-butylammonium fluoride (TBAF) in MeCN at room temperature to give (+)-hernandulcin **1** ($[\alpha]_D^{25}$ 104.0 (c 0.8, EtOH), lit. $[\alpha]_D^{25}$ +109 (*c* 0.11, EtOH),[2] lit. $[\alpha]_D^{20}$ +122 (*c* 0.111, EtOH),[5] lit. $[\alpha]_D^{26}$ +110.5 (*c* 0.11, EtOH)[7]) in 92% yield. The spectral data were in agreement with those already reported.

In summary, (+)-hernandulcin has been enantiospecifically synthesized in seven steps from (+)-neoisopulegol in a 25% overall yield (18% overall yield from (−)-isopulegol). This synthetic strategy might be useful for the preparation of other sesquiterpenes such as **4**, which has been isolated in an amount too small to be tasted as sweeteners.

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