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Synthesis of (+)-8-Deoxyvernolepin

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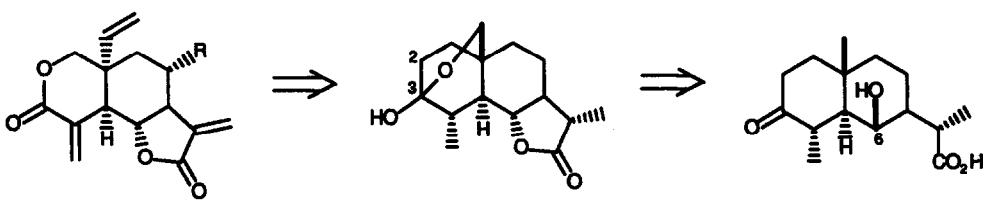
Abstract: *A short and efficient synthesis of (+)-8-deoxyvernolepin 2 from (-)-α-santonin, by functionalization of the angular methyl from a 6β-alkoxy radical generated by reaction of the alcohol with diphenylselenium hydroxyacetate and 1,4-fragmentation of a γ-hydroxylstannane using hypervalent organoiodine reagents as the key steps, is described. The most important structural features of this compound, the δ-valerolactone cis-fused to ring B moiety and the angular vinyl group, are introduced in the same step.*

The elemane sesquiterpene dilactone (+)-vernolepin **1**[1] possesses a synthetically interesting 2-oxa-*cis*-decalin unit having an angular vinyl group. This feature and its remarkable cytotoxic and antitumoral activity have stimulated several synthetic approaches and total syntheses.[2]

(+)-8-Deoxyvernolepin **2** that presents more potent activity against tumor cells *in vitro* cultures than the naturally occurring (+)-vernolepin[3a] has also been synthetized first in racemic[3] and more recently in optically active form.[4] All these procedures require in the key step cleavage by ozonolysis of ring A of a *trans*-fused decalin and then the δ-valerolactone moiety and angular vinyl group are accomplished in multi-step sequences.



1 Vernolepin, R = OH
2 Deoxyvernolepin, R = H

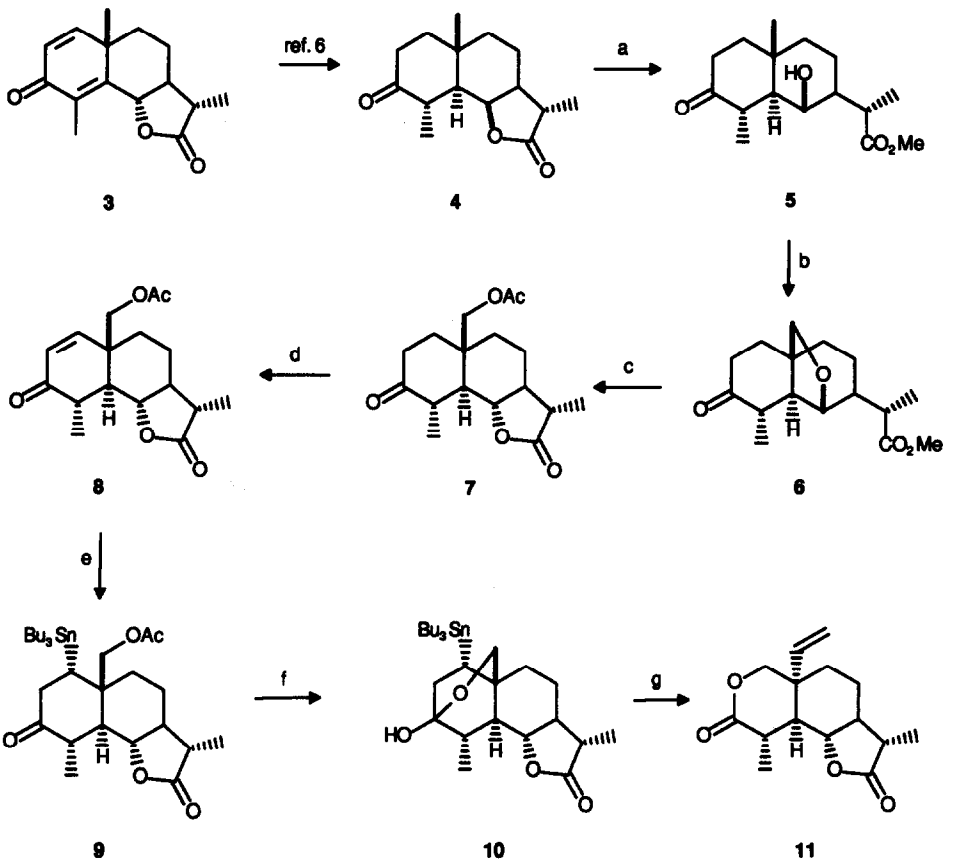
12

5

Scheme 1

In this communication we describe a short and efficient synthesis of (+)-8-deoxyvernolepin **2** in which the *cis*-fused δ-valerolactone AB-ring system and the angular vinyl group were accomplished, in excellent yield, in the same step. In our approach the key steps are: the functionalization of the angular methyl group at C-10 by hydrogen abstraction promoted by an alkoxy radical generated at C-6 and the regioselective cleavage of the C_2-C_3 bond by β-fragmentation of an alkoxy radical at C-3 (Scheme 1). In both cases the reagents and methodology have been developed recently in this laboratory.[5]

The starting point of our synthesis was β-tetrahydrosantonin **4** which was prepared from α-santonin by the known two-step procedure.[6] α-Santonin, a commercially available sesquiterpene and its hydro derivatives



Reagents and Conditions: (a) (i) NaOH (10 equiv), H_2O, reflux, 1h; (ii) 5% aqueous HCl; (iii) CH_2N_2 (excess), CH_2Cl_2, 62% overall. (b) $Ph_2Se(OH)OAc$ (2 equiv), I_2 (1 equiv), cyclohexane, hv (2x80 W tungsten-filament lamps), reflux, 3h, 84%. (c) ZnI_2 (1.6 equiv), Ac_2O, rt, 72 h, 100%. (d) (i) PhSeCl (1.75 equiv), BF_3.etherate (20 equiv), THF, rt, 100%; (ii) H_2O_2, 30% (0.38 ml), acetone, 0 °C to rt, 5 h, 80%. (e) Bu_3SnLi (4 equiv), THF, -78 °C, 6 h, 87%. (f) KOH (5 equiv), MeOH, rt, 30 min, 90%. (g) $PhI(OAc)_2$ (1.5 equiv), I_2 (0.8 equiv), cyclohexane, hv (2x80 W tungsten-filament lamps), 40 °C, 35 min, 100 %.

have been frequently employed as useful chiral starting materials for the synthesis of a variety of sesquiterpenoids.[2a]

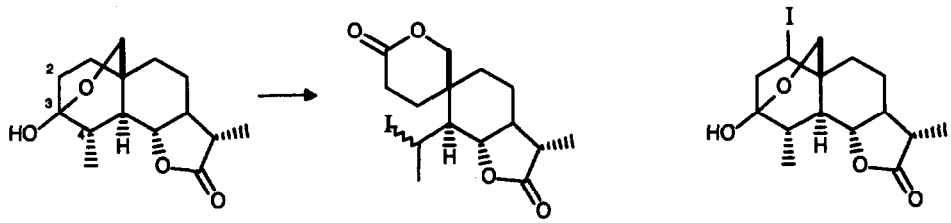
β-Tetrahydrosantonin **4** on treatment with 3% aqueous NaOH, careful neutralization with 5% aqueous HCl, and excess of ethereal diazomethane provided the 6β-hydroxy-ester **5** in 61% yield. Functionalization of the angular methyl group from the 6β-alkoxy radical was carried out under the conditions summarized in the Table (entries 1-2). Irradiation of a cyclohexane solution of **5** with visible light in the presence of (diacetoxyiodo)benzene (DIB)[5a] and iodine gave the epoxy-ester **6** in good yield. A better yield was obtained when the reaction was performed with diphenylselenium hydroxyacetate as oxidant agent.[7] An analogous 6,14-oxolane has been obtained as a by-product in low yield (5 %) in the synthesis of rishitin, using the Barton reaction by photolysis of the corresponding 6-nitrite.[8]

Table. Alkoxy Radical Reactions[a]

Entry	Substrate	Reagent	Conditions		Products
			Temp. (°C)	Time (h)	(Yields %)
1	**5**	DIB/I_2 (1.5/1)	40-43	5	**6** (65)
2	**5**	$Ph_2Se(OH)OAc/I_2$ (2/1)	reflux	3	**6** (84)
3	**12**	DIB/I_2 (1.5/0.8)	40-42	0.5	**13** (100)
4	**12**	HgO/I_2 (1.5/0.8)	reflux	1.5	**13** (100)
5	**10**	DIB/I_2 (1.5/0.8)	40-42	0.5	**11** (70), **14** (19)
6	**10**	DIB/I_2 (1.5/0.8)[b]	40-42	0.5	**11** (100)

[a]All reactions were performed in cyclohexane under irradiation with two 80 W tungsten-filament lamps. [b]A stream of oxygen was bubbled through the reaction mixture. DIB = (diacetoxyiodo)benzene.

Upon treatment of **6** with acetic anhydride and zinc iodide[9] regioselective cleavage of the C_6-O bond of the tetrahydrofuran ring occurred with concomitant lactonization and inversion of configuration to give as the sole product the 14-acetate derivative **7**.



12 **13** **14**

Scheme 2

The hemiacetal **12** obtained by hydrolysis of acetate **7** was treated with DIB/I_2[5b] (entry 3) or HgO/I_2 (entry 4) in order to study the regioselectivity of the β-fragmentation of the 3-alkoxy radical. As expected, the cleavage occurs exclusively at the C_3-C_4 bond to give the undesirable 4-iodo-spiro-δ-valerolactone **13**, no products derived from the cleavage of the C_2-C_3 bond being detected in any case (Scheme 2). In order to avoid this undesirable β-fragmentation reaction we proceeded as follows: phenylselenylation of **7**, with PhSeCl in the presence of boron trifluoride etherate,[10] followed by oxidative deselenylation (30 % H_2O_2), gave the enone **8** in 80 % yield, which by Michael addition of lithium tributyltin[11] (generated from hexabutylditin and metallic lithium[12]) gave the β-keto-stannane derivative **9**, and subsequent hydrolysis of the acetyl group produced the hemiacetal **10**. Oxidative 1,4-fragmentation[13] of hemiacetal **10** was performed by photolysis with visible light in the presence of DIB/I_2 (entry 5) to give (+)-8-deoxytetrahydrovernolepin **11** and the iodo-derivative **14** in 70 and 19 % yield, respectively. Since the substitution of the tributyltin group by iodine is a radical process that is inhibited by oxygen[14] if the photolysis is performed bubbling oxygen through the reaction mixture, complete regioselectivity in the β-fragmentation and quantitative yield of compound **11** were obtained (entry 6).

Conversion of (+)-8-deoxytetrahydrovernolepin **11** into (+)-8-deoxyvernolepin **2** has been previously accomplished,[4] and therefore the procedure followed constitutes the formal synthesis of the title compound.

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