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Synthesis of (+)-8-Deoxyvernolepin

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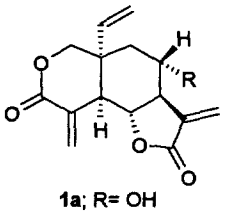
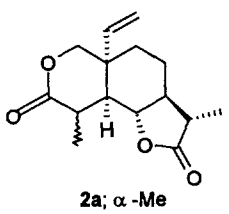
Abstract: The synthesis of (+)-8-deoxyvernolepin **1b** was accomplished by a short and efficient route from arsantin **5**. The key step involves a drastic rearrangement of an iodomesylate intermediate **4a** by the action of zinc. © 1997 Elsevier Science Ltd.

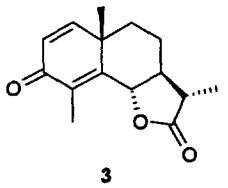
Vernolepin **1a** is an elemanolide with intense antitumoural activity,[1] whose 8-deoxyderivative, **1b**, is even more active against human lymphoblast leukaemia in "in vitro" cell cultures.[2] The above-mentioned properties have prompted the synthesis of both compounds,[3] 8-deoxyvernolepin **1b** being almost always prepared from **2a** by bis-olefination.



1a; R= OH
1b;R= H



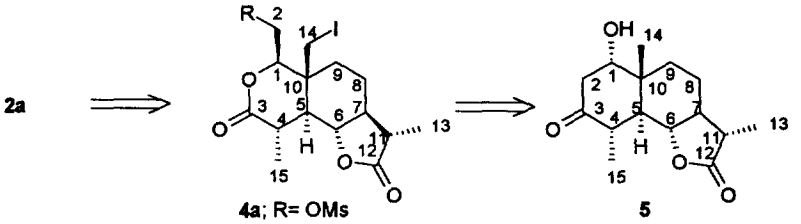
2a; α -Me
2b; β- Me



3

We have carried out the syntheses of **2a** and **2b** from arsantin **5**, a natural eudesmanolide that can be obtained in good yield from commercial α-santonin **3**.[4]

SCHEME 1



2a

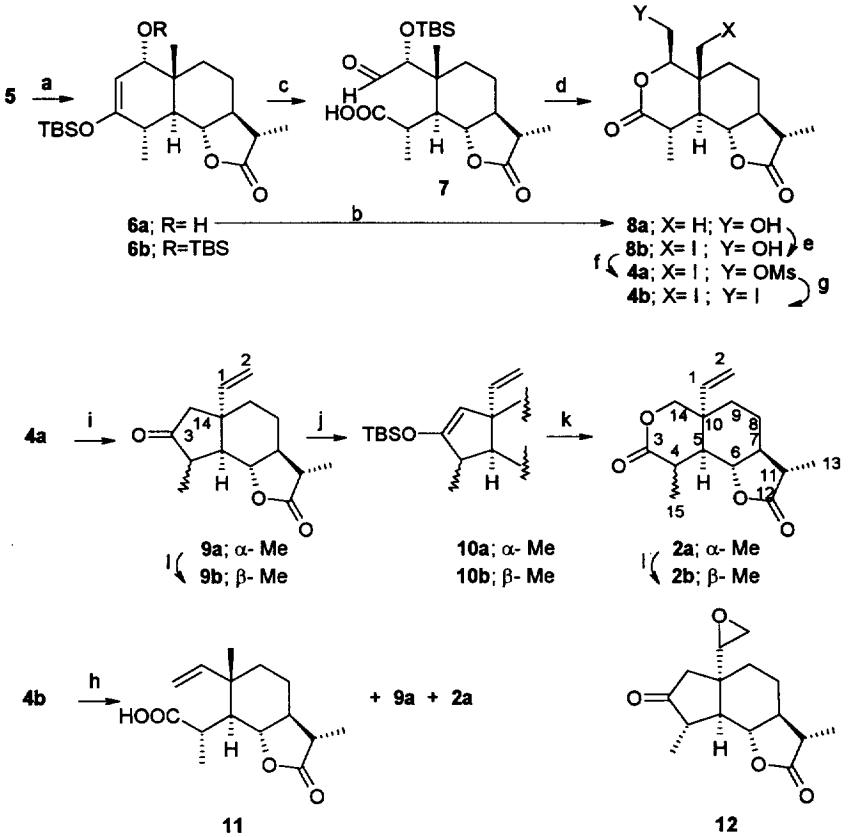
4a; R= OMs
4b; R= I

5

The methodology employed (Scheme 1) is based on the preparation of **4b** in order to induce, by the action of zinc, the elimination of the β-haloester system to generate the vinyl group at C_{10} and a carboxylate group at C_4. An intramolecular S_N2 reaction with an iodine displacement at C_{14}, by the carboxylate group would lead to a new δ-lactone ring and thus to **2a**.

Compound **4b** was formed as follows (Scheme 2): The enolization under kinetic conditions of 5[5] in the presence of TBSCl led to the silylenolethers **6a** and **6b** (93%; 3: 1). The reductive ozonolysis of the enol **6a** afforded **8a** (87%), while the transformation of the enol **6b** into **8a** was achieved in good yield (81%) via ozonolysis followed by hydrogenation with Adam's catalyst in HOAc of the aldehyde **7**.

SCHEME 2



Conditions: a- LDA, TBSCl, THF-HMPA, -78°C to rt (93%, ratio **6a**: **6b**, 3:1). b- i) O_3, MeOH-CH_2Cl_2, -78°C; ii) $NaBH_4$, -78°C to rt; H^+ (87%). c- i) O_3, MeOH- CH_2Cl_2, -78°C; ii) Me_2S, -78°C to rt (91%). d- i) H_2, PtO_2, HOAc; ii) HOAc-H_2O (3: 1), Δ (88%). e- IBDA- I_2, cyclohexane-CH_2Cl_2 (3: 1), 15-20 °C (85%). f- MsCl-pyridine, 0°C (98%). g- NaI, acetone, reflux (83%). h- Zn- HOAc- H_2O, THF (84%; ratio **11**: **9a**: **2a** ca 5: 2: 1). i- Zn- NaI- H_2O, DME, reflux (78%). j- LDA, TBSCl, THF-HMPA, -78°C to rt (93% from **9a** and 90% from **9b**). k- i) O_3 (1 equiv), MeOH- CH_2Cl_2, -78°C; ii) $NaBH_4$, -78°C to 0°C then H^+ (85% from **10a** and 72% from **10b**). l- DBN, benzene, 60°C (ratio **9a**: **9b** ca 1: 3; ratio **2a**: **2b** ca 1.5: 1).

The lactone **8a** has the hydroxymethyl group at C_1 β-equatorial (positive NOE effect between H_1 and H_5), suitably located for functionalization at C_{14}. Thus, treatment of **8a** with iodosylbenzene diacetate IBDA)/I_2, under irradiation with visible light,[6] afforded **8b** as the major product (85%),[7] which by mesylation followed by treatment with NaI in acetone led to **4b** (81%).

Treatment of **4b** with $Zn/HOAc/H_2O$, in THF or DME, afforded the acid **11** (53%), the ketone **9a** (21%) and the target compound **2a** (10%). The formation of this mixture indicates the low degree of selectivity of the attack (3:1 at C_2 and C_{14}, respectively); the acid **11** was formed by opening of the δ-valerolactone ring [8] with reduction of the iodomethyl group at C_{14}. The ketone **9a** was derived from the attack by zinc at C_{14}, and it is noteworthy that, during the process, the cleavage of two σ bonds, as well as the formation of a σ bond and a π one take place. The rearrangement is similar to the opening process of α-iodoepoxides, due to the action of zinc, to generate allylic alcohols.[9]

In view of the small yield of **2a** and considering that the ketone **9a** is readily transformed into the target compound, we decided to employ **4a** as starting material, since a preferential attack of zinc at C_{14} could be expected. In fact, treatment of **4a** with Zn/NaI in DME containing a few drops of water afforded **9a** (78%). The reaction sequence seemed to involve the iodine abstraction at C_{14} with an attack at C_3 and opening of the lactone ring favoured by expulsion of the mesyloxy group at C_2, that would give place to an intermediate epoxide, subsequently reduced to a vinyl group. The hypothesis is supported by the isolation of the epoxide **12** with short reaction times.[10]

Ketone **9a** was readily converted into 8-desoxytetrahydrovernolepin **2a** via the formation of its kinetic silylenolether and reductive ozonolysis of this last product, using 1 equivalent of ozone and $NaBH_4$ as reducing agent (79%).[11]

Compounds having physical and spectroscopical characteristics identical with those of **2a** have been synthesized previously. In some cases (Fujimoto [12a] and Yoshikoshi[12b]) the stereochemistry proposed for the methyl group at C_4 is β, while in another (Suárez [3b]) that orientation is α. In order to determine unequivocally the correct stereochemistry of **2a**, we decided to synthesize its epimer at C_4, that can be readily prepared from the ketone **9b**.

Indeed, base treatment of **9a** led to a mixture of epimeric ketones at C_4 (**9a**: **9b**)[13] in an approximate ratio of 1:3. The ketone **9b** was transformed into the lactone **2b** (65%) by means of a sequence described earlier for the formation of **2a**. On the other hand, base treatment of **2a**, under conditions identical with those of **9a**, led to a mixture of epimeric lactones at C_4 (**2a**: **2b**),[14] with an approximate composition of 1.5: 1.

The stereochemistry of the compounds obtained was confirmed by a thorough study of their NMR spectra. These results clearly indicated that the previously synthesized (+)-desoxytetrahydrovernolepin [3a,12] has the methyl group at C_4 in α position, in good agreement with the proposal of Suárez et al.[3b]

Conversion of **2a** into (+)-8-deoxyvernolepin **1b** has been previously accomplished,[12] and therefore the procedure followed constitutes a formal synthesis of the title compound.

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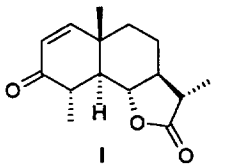
5. In this reaction, the simultaneous addition of the mixture of arsantin and TBSCl to LDA is crucial, otherwise significant amounts of the enone I are obtained.



I

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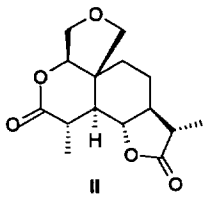
7. Small amounts of the ether **II** are detected, that may be obtained by way of the halohydrin **8b** by treatment with anhydrous NaOAc in HMPA. Likewise, **II** is the major product resulting from the irradiation of **8a** in benzene, with visible light, in the presence of lead tetraacetate



II

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10. All compounds showed analytical and spectral data consistent with their structures. **12**, ^{1}H-nmr ($CDCl_3$), δ ppm: 3.70 (1H, dd, J= 10.8, 10.8 Hz, H_6), 2.94 (1H, dd, J= 3.5, 3.2 Hz, H_2), 2.73 (1H, dd, J= 4.0, 4.0 Hz, H_1), 2.49 (2H, c, H_{2*} + H_4), 1.36 (3H, d, J= 7.7 Hz, H_{15}), 1.27 (3H, d, J= 7.0 Hz, H_{13}).
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13. **9a**, ^{1}H-nmr ($CDCl_3$), δ ppm: 5.84 (1H, dd, J= 10.7, 17.7 Hz, H_1), 5.11 (1H,d, J= 10.7 Hz, H_2), 5.04 (1H, d, J= 17.6 Hz, H_{2*}), 3.73 (1H, dd, J= 10.8, 10.9 Hz, H_6), 2.52 (1H,d, J= 17.6 Hz, H_{14}), 2.44 (1H,d, J= 17.8 Hz, H_{14*}), 2.43 (1H, c, H_4), 2.31 (1H, dq, J= 12.3, 6.8 Hz, H_{11}), 2.01 (1H, d, J= 10.6 Hz, H_5), 1.26 (3H, d, J= 6.9 Hz, H_{13}), 1.20 (3H, d, J= 7.7 Hz, H_{15}). ^{13}C-nmr ($CDCl_3$): 146.20 (C_1), 113.83 (C_2), 218.25 (C_3), 47.14 (C_4), 52.14 (C_5), 84.96 (C_6), 49.33 (C_7), 23.69 (C_8), 34.00 (C_9), 45.64 (C_{10}), 41.46 (C_{11}), 178.63 (C_{12}), 12.58 (C_{13}), 44.52 (C_{14}), 17.67 (C_{15}). Positive NOE of H_6 with H_4 , H_{11}, and H_5 with H_1 , H_{15}. **9b**, ^{1}H-nmr ($CDCl_3$), δ ppm: 5.87 (1H, dd, J= 10.8, 17.3 Hz, H_1), 5.14 (1H, d, J= 10.7 Hz, H_2), 5.06 (1H, d, J= 17.4 Hz, H_{2*}), 3.56 (1H, dd, J= 10.8, 10.8 Hz, H_6), 2.68 (1H, dq, J= 7.1, 7.1 Hz, H_4), 2.41 (1H, d, J= 19.1 Hz, H_{14}), 2.31 (1H, dd, J= 7.2, 10.3 Hz, H_5), 2.27 (1H, d, J= 19.1 Hz, H_{14*}), 2.24 (1H, dq, J= 6.8, 12.4 Hz, H_{11}), 1.25 (3H, d, J= 6.9 Hz, H_{13}), 1.16 (3H, d, J= 7.3 Hz, H_{15}).^{13}C-nmr ($CDCl_3$): 145.36 (C_1), 113.39 (C_2), 217.66 (C_3), 46.95 (C_4), 49.44 (C_5), 81.80 (C_6), 50.50 (C_7), 22.94 (C_8), 34.32(C_9), 44.83 (C_{10}), 40.38 (C_{11}), 178.80 (C_{12}), 12.45 (C_{13}), 42.57 (C_{14}), 10.68 (C_{15}). Positive NOE of H_5 with H_4 , H_1 , and H_6 with H_{11} , H_{15}).
14. **2a**, mp 130-132 °C (lit. [13a] 130-132°C, lit. [13b] 127-129°C); $[\alpha]_D$ = + 35.6 ° (c= 0.3 , $CHCl_3$) (lit. [3b] : + 37 °, lit [13b] : + 47.7 °). ^{1}H-nmr ($CDCl_3$), δ ppm: 5.78 (1H, dd, J= 10.9, 17.6 Hz, H_1), 5.28 (1H, d, J= 10.9 Hz, H_2), 5.24 (1H, d, J= 17.6 Hz, H_{2*}), 4.38 (1H, d, J= 11.7 Hz, H_{14}), 4.14 (1H, dd, J= 11.7, 1.12 Hz, H_{14*}); 3.99 (1H, dd, J= 10.8, 10.8 Hz, H_6), 2.70 (1H, dq, 7.1, 5.2 Hz, H_4), 2.32 (1H, dq, J= 12.3, 6.9 Hz, H_{11}), 1.95(1H, dd, J= 10.3, 5.0 Hz, H_5), 1.40 (3H, d, J= 7.2 Hz, H_{15}), 1.25 (3H, d, J= 7.0 Hz, H_{13}). Positive NOE of H_6 with H_4, H_{11}, and H_5 with H_1 , H_{15}. ^{13}C-nmr ($CDCl_3$): 142.18 (C_1), 115.56 (C_2), 173.62 (C_3), 37.31 (C_4), 46.63 (C_5), 83.75 (C_6), 48.42 (C_7), 22.90(C_8), 31.71 (C_9), 41.78 (C_{10}), 41.36 (C_{11}), 178.16 (C_{12}), 12.47 (C_{13}),71.56 (C_{14}), 17.65 (C_{15}). **2b**, oil, $[\alpha]_D$ = + 4.5° (c= 0.3, $CHCl_3$). ^{1}H-nmr ($CDCl_3$), δ ppm: 5.81 (1H, dd, J= 10.8, 17.6 Hz, H_1), 5.33 (1H, d, J= 17.5 Hz, H_2), 5.33 (1H, d, J= 10.8 Hz, H_{2*}), 4.31 (1H, d, J= 12.3 Hz ,H_{14}), 4.14 (1H, d, J= 12.3 Hz, H_{14*}), 3.90 (1H, dd, J= 10.8, 10.8 Hz, H_6), 2.94 (1H, apparent quintuplet, J= 6.8, 6.7, 7.0 Hz , H_4), 2.15 (2H, m, H_{11}+H_5), 1.38 (3H, d, J= 7.2 Hz, H_{15}), 1.22 (3H, d, J= 6.9 Hz, H_{13}). ^{13}C-nmr ($CDCl_3$): 142.18 (C_1), 115.89 (C_2), 173.06 (C_3), 35.83 (C_4), 46.88 (C_5), 80.03 (C_6), 48.92 (C_7), 22.26 (C_8), 30.54 (C_9), 42.43 (C_{10}), 40.84 (C_{11}), 178.41 (C_{12}), 12.50 (C_{13}), 71.21 (C_{14}), 14.15 (C_{15}). Positive NOE of H_5 with H_4, H_1, and H_6 with H_{11}, H_{15}.

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