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Synthesis of Elemane *bis*-Lactones Structurally Related to Vernolepin

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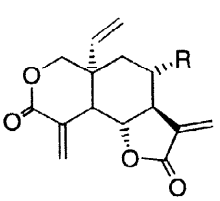
Abstract: The chemical transformation of santonin into an elemane *bis*-lactone structurally related to the antitumour compound vernolepin is reported. The transformation of ring A of santonin into a hemiacetal δ-lactone was achieved in eleven steps. The spectroscopic characteristics of the synthetic product obtained in this way revealed that the proposed structure for the natural product should be revised.

Sesquiterpene lactones constitute a group of natural compounds widely distributed in the plant kingdom.[1,2] Some of these lactones exhibit a remarkable range of biological activities, which include cytotoxic, antibacterial, antifeedant and antitumoural properties.

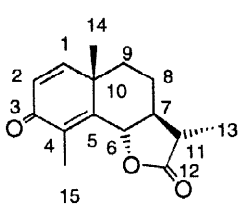
Although the majority of these sesquiterpene lactones have only one γ-lactone moiety in their structure, normally positioned between the C_6-C_{12} or C_8-C_{12} carbon atoms, a smaller number of *bis*-lactones incorporating an additional δ-lactone moiety have been described as natural products.

Some examples are the potent antitumour elemane *bis*-lactones vernolepin (**1**)[3] and its C_8 deoxyderivative deoxyvernolepin (**2**) which shows an even stronger activity against tumour cells *in vitro*. This biological activity has prompted a few syntheses of 8-deoxyvernolepin (**2**), most of them using santonin (**1**) as starting material.[4-9]

On the other hand, the isolation of a natural product **4** structurally related to the former ones, which incorporates a δ–lactone on the A ring too, from *Artemisia judaica* has been reported.[10] This compound shows a unique structural feature consisting in a hemiacetal δ–lactone moiety between a carboxylate group on C_3 and a



1 R = OH
2 R = H



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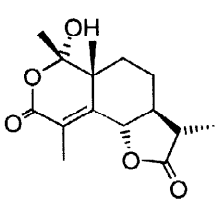

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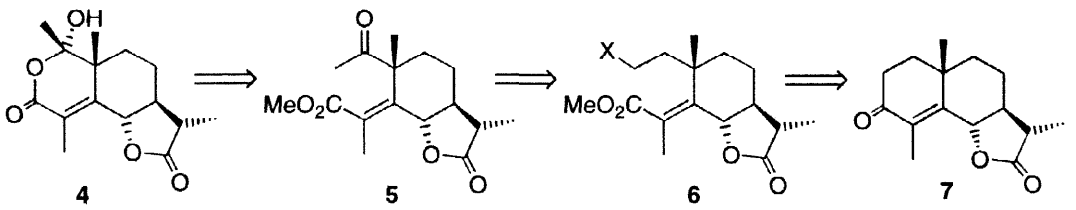
ketone hydrate on C_1. This unique structural feature together with the antitumour properties of the elemane *bis*-lactone 8-deoxyvernolepin and the structural similarity between both products prompted us to undertake the synthesis of compound **4** starting from santonin (**1**).

The retrosynthetic analysis of compound **4** led to a ketoester **5**, which could be obtained, in principle, from a C_2 functionalised elemane derivative **6**, and this could be obtained in turn from dihydrosantonin (**7**) after cleavage of the C_2-C_3 bond.

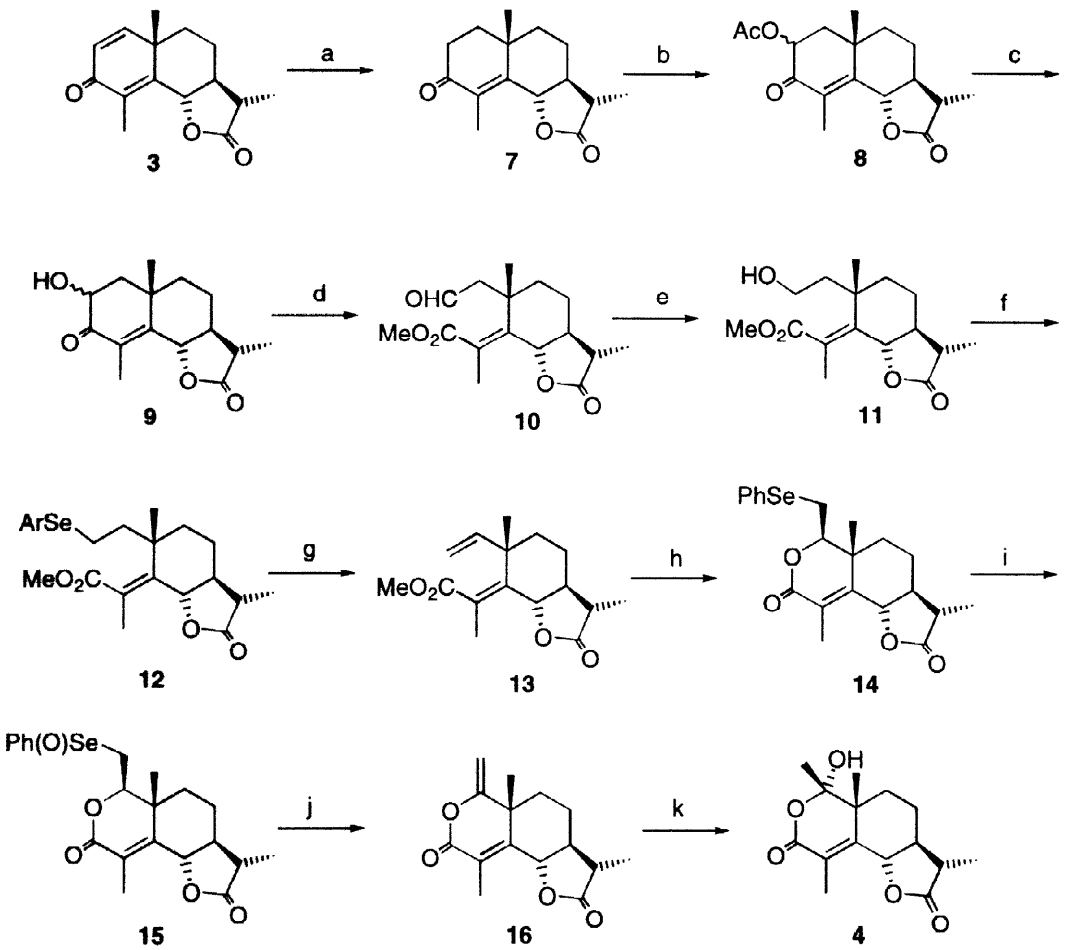


In order to cleave the C_2-C_3 bond, dihydrosantonin (**7**), obtained by hydrogenation of santonin (**3**) with the Wilkinson catalyst, was acetoxylated on C_2 by treatment with lead tetraacetate to give a mixture of two epimeric acetates **8**.[4] Methanolysis of this mixture with *p*-toluenesulphonic acid in methanol afforded the corresponding alcohol mixture **9** in 95 % yield, which allowed cleavage of the C_2-C_3 bond upon treatment with lead tetraacetate in hexane:methanol (1:3).[11] The resulting aldehyde-ester **10** was very unstable and therefore, was immediately reduced with sodium borohydride to give alcohol **11** in 67% overall yield for the two steps.

Functionalisation of the C_1 carbon was achieved by elimination of the C_2 hydroxyl group in two steps involving transformation of the hydroxyl group into an *o*-nitrophenylselenide **12** in 84% yield followed by elimination of the corresponding selenoxide upon treatment with H_2O_2 to give **13** in 89% yield.[12]

With compound **13** in hand we attempted the introduction of a carbonyl group on C_2. Alkene **13** was subjected to several Wacker reaction modified procedures[13,14] which were unsuccessful. Other procedures for the hydration of the C_1-C_2 double bond such as oxymercuration[15] were equally unsuccessful.

These results prevented our initial idea of using ketoester **5** as intermediate in the synthetic sequence. To overcome this problem we planned a new strategy consisting of the introduction of a hydroxyl group on C_2 and a potential leaving group on C_1 which after elimination would yield an enol derivative synthetically equivalent to a carbonyl group on C_2. Thus treatment of alkene **13** with PhSeCl in aqueous acetonitrile[16] gave a *bis*-lactone **14** with total regio- and stereoselectivity. NOE was observed between H_1 (δ 4.18) and $H_{9\alpha}$ (δ 1.21) indicating the α orientation of H_1. Treatment of **14** with H_2O_2 gave the corresponding selenoxides **15** in 90% yield. Despite the fact that elimination of selenoxides usually occurs at room temperature, in our case elimination was only observed after heating at benzene reflux temperature to give the corresponding enol-lactone **16** in 93% yield. Eventually, hydration of the double bond with 50% H_2SO_4 afforded the desired product **4** in 86% yield.[1] The stereochemistry of C_1 was assigned on the basis of an NOE observed between H_2 (δ 1.57) and H_{14} (δ 1.30).



Reagents and conditions: a) H_2,benzene, Wilkinson Catalyst (100%); b) $Pb(OAc)_4$ (1.5 mmol), AcOH, 80°C, 20h(65%); c) *p*-TsOH (cat.), MeOH, reflux, 5h (95%); d) $Pb(OAc)_4$ (1.5 mmol), 1:3 MeOH:Hexane, r.t., 25 min; e) $NaBH_4$ (0.5 mmol), MeOH, 0°C, 25 min (67% overall from **9**); f) *o*-$NO_2C_6H_4SeCN$ (1.5 mmol)- Bu_3P (1.5 mmol), 1:1 THF:py, r.t., 1h (84%); g) 30 % H_2O_2 (3.5 mmol), THF, 0°C to r.t., 7h (89%); h) PhSeCl (1.1 mmol), 5:1 CH_3CN:H_2O, r.t., 2h (93%); i) 30 % H_2O_2 (5.5 mmol), THF, 0°C to r.t., 2h (90%); j) Benzene, reflux, 30 min (90%); k) 50% H_2SO_4, r.t. 45 min (86%)

The synthetic material obtained in this way showed spectral data consistent with its structure, however, these spectral data do not coincide with those reported in the literature for the natural product isolated from *Artemisia judaica*, indicating that the structure of this natural product should be revised.

Further work on the application of this methodology to the synthesis of other *bis*-lactones and the use of derivatives of compound **14** to functionalise C_{14}[9] in the synthesis of vernolepin derivatives are in progress.

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[1] Compound **4**: m.p. 188-199 °C; $[\alpha]_D^{21}$ +210 (Cl_3CH, *c* 0.8); IR (KBr) 3550-3275, 1777, 1698 cm^{-1}; MS *m/e* 280 (M^+, 100), 262 (M^+-H_2O, 7), 207 (45); HRMS 280.1306 $C_{15}H_{20}O_5$ required 280.1311; ^1H NMR (400 MHz, Cl_3CD) δ 1.27 (d, 3H, *J* = 7.0 Hz, H_{13}), 1.30 (s, 3H, H_{14}), 1.52 (dq, 1H, *J* = 4. 12.5 Hz, $H_{8\beta}$), 1.57 (s, 3H, H_2), 1.70 (ddd, 1H, *J* = 2.4, 4.0, 12.5 Hz, $H_{9\beta}$), 1.95 (dt, 1H, *J* =3.0, 12.5 Hz, H_7), 2.05 (m, 1H, $H_{8\alpha}$), 2.14 (2, 3H, *J* = 2.0 Hz, H_{15}), 2.18 (dt, 1H, *J* = 5.0, 12.5 Hz, $H_{9\alpha}$), 2.33 (dq, 1H, *J* = 7.0, 12.5 Hz, H_{11}), 3.74 (s, 1H, OH), 4.60 (qd, 1H, *J* = 2.0, 11.6 Hz, H_6); ^1H NMR (400 MHz, C_6D_6, main peaks) δ 0.75 (s, 3H, H_{14}), 0.86 (d, 3H, *J* = 6.4 Hz, H_{13}), 1.28 (s, 3H, H_2), 2.41 (d, 3H, *J* = 1.2 Hz, H_{15}), 3.71 (qd, 1H, *J* = 1.2, 11.6 Hz, H_6); ^{13}C NMR (100 MHz, Cl_3CD) δ 12.3 (q), 13,1 (q), 22.9 (t), 23.8 (t), 23.8 (q), 33.0 (t), 40.8 (d), 44.7 (s), 50.5 (d), 80.9 (d), 104.1(s), 121.3 (s), 147.2 (s), 164.9 (s), 177.5 (s).