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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  $\delta$ -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. © 1998 Elsevier Science Ltd. All rights reserved.

Sesquiterpene lactones constitute a group of natural compounds widely distributed in the plant kingdom.<sup>1,2</sup> 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  $\gamma$ -lactone moiety in their structure, normally positioned between the C<sub>6</sub>-C<sub>12</sub> or C<sub>8</sub>-C<sub>12</sub> carbon atoms, a smaller number of *bis*-lactones incorporating an additional  $\delta$ -lactone moiety have been described as natural products.

Some examples are the potent antitumour elemane *bis*-lactones vernolepin  $(1)^3$  and its C<sub>8</sub> 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.<sup>4-9</sup>

On the other hand, the isolation of a natural product 4 structurally related to the former ones, which incorporates a  $\delta$ -lactone on the A ring too, from *Artemisia judaica* has been reported.<sup>10</sup> This compound shows a unique structural feature consisting in a hemiacetal  $\delta$ -lactone moiety between a carboxylate group on C<sub>3</sub> and a



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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.<sup>4</sup> 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).<sup>11</sup> 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<sub>2</sub>O<sub>2</sub> to give **13** in 89% yield.<sup>12</sup>

With compound 13 in hand we attempted the introduction of a carbonyl group on C<sub>2</sub>. Alkene 13 was subjected to several Wacker reaction modified procedures<sup>13,14</sup> which were unsuccessful. Other procedures for the hydration of the C<sub>1</sub>-C<sub>2</sub> double bond such as oxymercuration<sup>15</sup> 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<sub>2</sub> and a potential leaving group on C<sub>1</sub> which after elimination would yield an enol derivative synthetically equivalent to a carbonyl group on C<sub>2</sub>. Thus treatment of alkene 13 with PhSeCl in aqueous acetonitrile<sup>16</sup> gave a *bis*-lactone 14 with total regio- and stereoselectivity. NOE was observed between H<sub>1</sub> ( $\delta$  4.18) and H<sub>9<sub>α</sub></sub> ( $\delta$  1.21) indicating the  $\alpha$  orientation of H<sub>1</sub>. Treatment of 14 with H<sub>2</sub>O<sub>2</sub> 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<sub>2</sub>SO<sub>4</sub> afforded the desired product 4 in 86% yield.<sup>1</sup> The stereochemistry of C<sub>1</sub> was assigned on the basis of an NOE observed between H<sub>2</sub> ( $\delta$  1.57) and H<sub>14</sub> ( $\delta$  1.30).



**Reagents and conditions:** a) H<sub>2</sub>, benzene, Wilkinson Catalyst (100%); b) Pb(OAc)<sub>4</sub> (1.5 mmol), AcOH, 80°C, 20h(65%); c) *p*-TsOH (cat.), MeOH, reflux, 5h (95%); d) Pb(OAc)<sub>4</sub> (1.5 mmol), 1:3 MeOH:Hexane, r.t., 25 min; e) NaBH<sub>4</sub> (0.5 mmol), MeOH, 0°C, 25 min (67% overall from 9); f) o-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>SeCN (1.5 mmol)- Bu<sub>3</sub>P (1.5 mmol), 1:1 THF:py, r.t., 1h (84%); g) 30 % H<sub>2</sub>O<sub>2</sub> (3.5 mmol), THF, 0°C to r.t., 7h (89%); h) PhSeCl (1.1 mmol), 5:1 CH<sub>3</sub>CN:H<sub>2</sub>O, r.t., 2h (93%); i) 30 % H<sub>2</sub>O<sub>2</sub> (5.5 mmol), THF, 0°C to r.t., 2h (90%); j) Benzene, reflux, 30 min (90%); k) 50% H<sub>3</sub>SO<sub>4</sub>, 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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<sup>1</sup> Compound 4: m.p. 188-199 °C;  $[\alpha]_{D}^{21}$  +210 (Cl<sub>3</sub>CH, *c* 0.8); IR (KBr) 3550-3275, 1777, 1698 cm<sup>-1</sup>; MS *m/e* 280 (M<sup>+</sup>, 100), 262 (M<sup>+</sup>-H<sub>2</sub>O, 7), 207 (45); HRMS 280.1306 C<sub>15</sub>H<sub>20</sub>O<sub>5</sub> required 280.1311; <sup>1</sup>H NMR (400 MHz, Cl<sub>3</sub>CD)  $\delta$  1.27 (d, 3H, *J* = 7.0 Hz, H<sub>13</sub>), 1.30 (s, 3H, H<sub>14</sub>), 1.52 (dq, 1H, *J* = 4. 12.5 Hz, H<sub>8p</sub>), 1.57 (s, 3H, H<sub>2</sub>), 1.70 (ddd, 1H, *J* = 2.4, 4.0, 12.5 Hz, H<sub>9p</sub>), 1.95 (dt, 1H, *J* = 3.0, 12.5 Hz, H<sub>7</sub>), 2.05 (m, 1H, H<sub>8a</sub>), 2.14 (2, 3H, *J* = 2.0 Hz, H<sub>15</sub>), 2.18 (dt, 1H, *J* = 5.0, 12.5 Hz, H<sub>3a</sub>), 2.33 (dq, 1H, *J* = 7.0, 12.5 Hz, H<sub>11</sub>), 3.74 (s, 1H, OH), 4.60 (qd, 1H, *J* = 2.0, 11.6 Hz, H<sub>6</sub>); <sup>1</sup>H NMR (400 MHz, C<sub>6</sub>D<sub>6</sub>, main peaks)  $\delta$  0.75 (s, 3H, H<sub>14</sub>), 0.86 (d, 3H, *J* = 6.4 Hz, H<sub>13</sub>), 1.28 (s, 3H, H<sub>2</sub>), 2.41 (d, 3H, *J* = 1.2 Hz, H<sub>15</sub>), 3.71 (qd, 1H, *J* = 1.2, 11.6 Hz, H<sub>6</sub>); <sup>13</sup>C NMR (100 MHz, Cl<sub>3</sub>CD)  $\delta$  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).