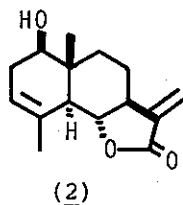
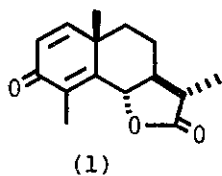


CHEMICAL TRANSFORMATION OF  $\alpha$ -SANTONIN INTO SESQUITERPENE  
 $\alpha$ -METHYLENE- $\gamma$ -LACTONES, DOUGLANINE, AND LUDOVICIN A AND B<sup>1</sup>

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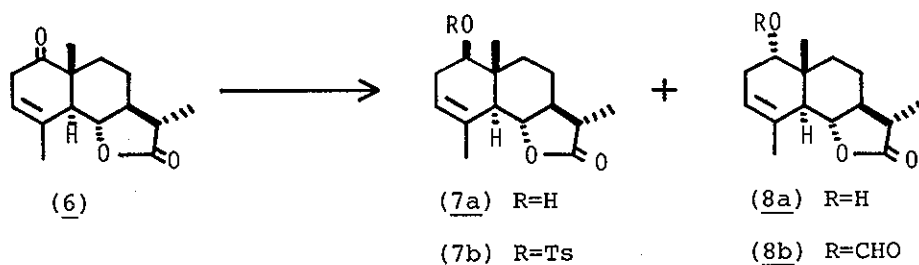
Eudesman type  $\alpha$ -methylene- $\gamma$ -lactones, douglanine (3), ludovicin A and B (4 and 5) have been synthesized from  $\alpha$ -santonin (1). Enone (6) was reduced with  $\text{LiAlH}(\text{OBU}^t)_3$  to give alcohols (7a) and (8a) in 6:1 ratio. Phenylselenenylation of 8a afforded a selenide (11). Oxidative elimination of 11 with 2 eq.  $\text{H}_2\text{O}_2$  gave douglanine (3), while 11 was treated with an excess  $\text{H}_2\text{O}_2$  to afford ludovicin A and B (4 and 5).

In the previous papers of this series, we reported the chemical transformation of  $\alpha$ -santonin (1) into sesquiterpene  $\alpha$ -methylene- $\gamma$ -lactones, tuberiferine,<sup>2</sup> artecalin,<sup>2</sup> arglanine,<sup>3</sup> santamarine (2),<sup>3</sup> yomogin,<sup>4</sup> balchanin,<sup>5</sup> and arbusculin A.<sup>5</sup> Some of these compounds showed antitumor and anti-inflammatory activities *in vitro* and *in vivo*.<sup>6</sup>



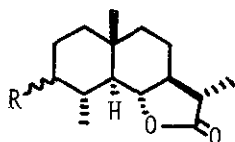
In this communication, we report the synthesis of douglanine (3) which is a 1-OH epimer of santamarine, ludovicin A and B (4 and 5).

Synthesis of an enone (6), mp 142-145°, as a key intermediate for santamarine (2) was reported from this laboratory.<sup>3</sup> Reduction of this enone (6) with NaBH<sub>4</sub> in MeOH at 0°C gave stereoselectively 1β-hydroxy compound (7a; 88.2% yield), mp 135.5-137°, together with 1α-hydroxy compound (8a; 2.7% yield), mp 139-141°.



Corey and Terashima<sup>7</sup> reported epimerization of hydroxyl groups by S<sub>N</sub>2 displacement of the tosylates of alcohols with tetrabutylammonium formate. When the reaction of the tosylate (9b), mp 143-145°, of the model compound, 3β-hexahydrosantonin (9a), with tetrabutylammonium formate was carried out in refluxing acetone for 16 hr, the desired 3α-formate (9c), mp 88-90° [IR: 1700 cm<sup>-1</sup>; NMR δ: 8.01 (1H, s, CHO), 5.05 (1H, 3-H)] was obtained in 78% yield. However, refluxing of the 1β-tosylate (7b), mp 162-164° [NMR δ: 5.2 (1H), 4.2 (t, J=7 Hz), 2.45 (s)] with tetrabutylammonium formate in acetone for 37 hr gave only unchanged starting material.

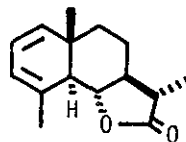
When the reaction was carried out in methyl ethyl ketone at refluxing temperature for 4 hr, a small amount of the eliminated product, a diene (10), mp 98-100°, was obtained but not the desired inverted formate (8b).



(9a) R=β-OH

(9b) R=β-OTs

(9c) R=α-CHO



(10)

Reduction of the enone (6) with lithium tri-*tert*-butoxyaluminum hydride gave a mixture of β-ol (7a) and α-ol (8a) in 73.6% and 12.4% yield, respectively. Pure products (7a and 8a) were separated by preparative TLC. α-ol (8a); IR: 1750, 3530; NMR δ: 1.84 (d,  $J=1.5$  Hz, 4-CH<sub>3</sub>), 3.40 (t,  $J=3$  Hz, 1-H), 5.25 (bs, 3-H).

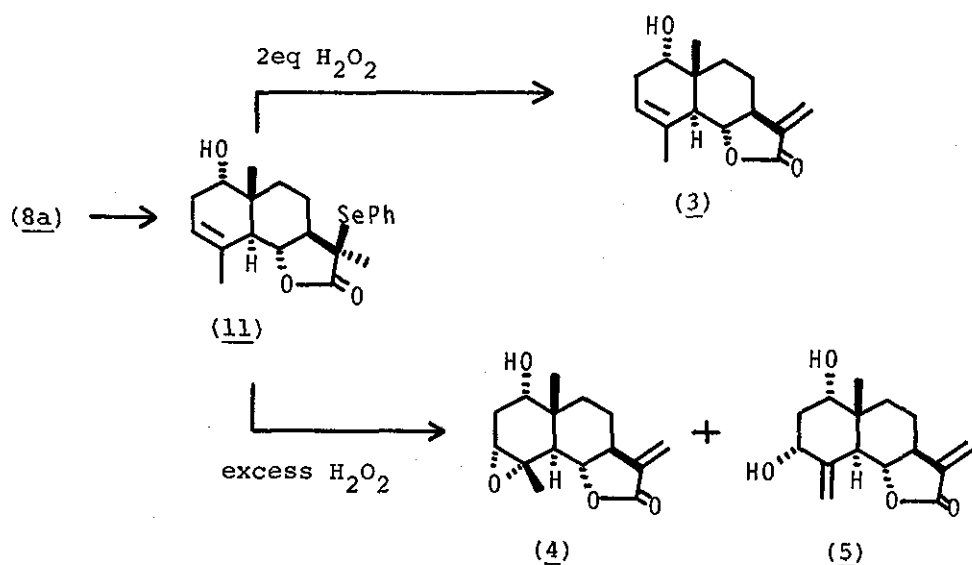
Phenylselenenylation of α-ol (8a), according to the procedure described by Grieco *et al.*,<sup>8</sup> gave a phenylselenide (11) as an oil [NMR δ: 1.52 (s, 11-CH<sub>3</sub>)]. Oxidation of the selenide (11) with 2 molar equivalents of 30% H<sub>2</sub>O<sub>2</sub> in THF-AcOH at 0°C produced a selenoxide as an intermediate which underwent facile *syn*-elimination to give an *exo*-methylene compound (3), mp 116-118° [Mass  $m/e$ : 248, M<sup>+</sup>;  $[\alpha]_D^{23}$  +153°; NMR δ: 0.80 (s, 10-CH<sub>3</sub>), 1.83 (bs, 4-CH<sub>3</sub>), 3.35 (bt,  $J=3$  Hz, 1-H), 3.92 (t,  $J=11$  Hz, 6-H), 5.33 (m, 3-H), 5.32, 6.00 (d,  $J=3$  Hz,  $\begin{matrix} \text{H} \\ \diagdown \\ \text{C} \\ \diagup \\ \text{H} \end{matrix}$ )]. The compound (3) was identified by comparing its

mp, IR, and NMR spectra with those of natural douglanine isolated from *Artemisia douglasiana* Bess by Matsueda and Geissman.<sup>9,10</sup>

On the other hand, oxidation of 11 with an excess (ca. 20 molar eq.) of 30% H<sub>2</sub>O<sub>2</sub> in THF-AcOH gave a mixture of *exo*-methylene compounds. Chromatographic separation of the products gave a compound (4), mp 215-217° (22% yield), and a compound (5), mp 156-157° (36% yield), but 3a was not formed in this condition. Compound (4): mass *m/e*: 264, M<sup>+</sup>, 249 (M-15)<sup>+</sup>, 246 (M-18)<sup>+</sup>, 231 (M-15-18)<sup>+</sup>; [α]<sub>D</sub><sup>23°</sup> +113° (CHCl<sub>3</sub>); NMR δ: 0.84 (s, 10-CH<sub>3</sub>), 1.47 (s, 4-CH<sub>3</sub>), 3.00 (t, *J*=1.5 Hz, 3-H), 3.20 (m, 1-H), 3.90 (dd, *J*=12, 11 Hz, 6-H), 5.35, 6.02 (d, *J*=3 Hz, <math>\begin{matrix} \text{H} \\ \diagdown \\ \text{H} \end{matrix}</math>); IR  $\nu_{\text{max}}^{\text{KBr}}$  cm<sup>-1</sup>: 3570, 1755, 1670. Compound (5): mass *m/e*: 264, M<sup>+</sup>, 246 (M-18)<sup>+</sup>; [α]<sub>D</sub><sup>23°</sup> +108° (CHCl<sub>3</sub>); NMR δ: 0.78 (s, 10-CH<sub>3</sub>), 3.40 (m, 1-H), 3.98 (t, *J*=11 Hz, 6-H), 4.38 (t, *W*<sup>1/2</sup>=8 Hz, 3-H), 5.02, 5.13 (bs, 4- <math>\begin{matrix} \text{H} \\ \diagdown \\ \text{H} \end{matrix}</math>), 5.36, 6.03 (d, *J*=3 Hz, 11- <math>\begin{matrix} \text{H} \\ \diagdown \\ \text{H} \end{matrix}</math>); IR  $\nu_{\text{max}}^{\text{KBr}}$  cm<sup>-1</sup>: 3300, 1770, 1755, 1650].

Grieco *et al.*<sup>11</sup> recently reported a similar fact that treatment of the phenylselenide of saussurea lactone with 2 equivalents of 30% H<sub>2</sub>O<sub>2</sub> gave dehydrosaussurea lactone, whereas with a large amount of 30% H<sub>2</sub>O<sub>2</sub> afforded a mixture of epoxy-dehydrosaussurea lactone and dehydrosaussurea lactone.

Compounds (4) and (5) were identified by comparing their mp, and IR, mass, and NMR spectra with those of natural ludovicin A (reported:<sup>12</sup> mp 215°, [α]<sub>D</sub> +128°), and NMR spectrum<sup>10</sup>) and ludovicin B (reported:<sup>12</sup> mp 152°, [α]<sub>D</sub> +138°), respectively, which had been isolated from *Artemisia ludoviciana* subsp. *mexicana* by Lee and Geissman.<sup>12</sup>



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