CHEMICAL TRANSFORMATION OF α-SANTONIN INTO SESQUITERPENE α-METHYLENE-γ-LACTONES, DOUGLANINE, AND LUDOVICIN A AND B[1]

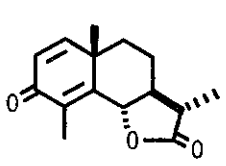
Koji Yamakawa,* Kiyoshi Nishitani, and Kazutoyo Azusawa**

Faculty of Pharmaceutical Sciences, Science University of Tokyo

Ichigaya-funagawara-machi, Shinjuku-ku, Tokyo 162, Japan

Eudesman type α-methylene-γ-lactones, douglanine (3), ludovicin A and B (4 and 5) have been synthesized from α-santonin (1). Enone (6) was reduced with $LiAlH(OBu^t)_3$ to give alcohols (7a) and (8a) in 6:1 ratio. Phenylselenenylation of 8a afforded a selenide (11). Oxidative elimination of 11 with 2 eq. H_2O_2 gave douglanine (3), while 11 was treated with an excess H_2O_2 to afford ludovicin A and B (4 and 5).

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



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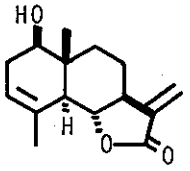
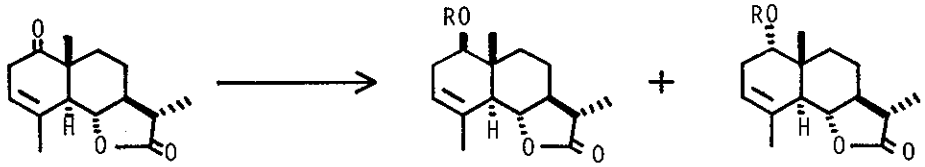


(2)

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.[3] Reduction of this enone (6) with $NaBH_4$ 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°.

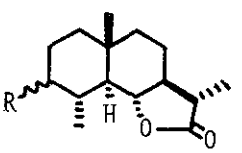


(6) (7a) R=H (8a) R=H

(7b) R=Ts (8b) R=CHO

Corey and Terashima[7] reported epimerization of hydroxyl groups by S_N2 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^{-1}; 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.

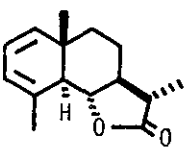
When the reaction was carried out in methyl ethyl ketone at refluxing temperature for 4 hr, a small amount of the eliminated product, a diene (10), mp 98-100°, was obtained but not the desired inverted formate (8b).



(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 1β-ol (7a) and 1α-ol (8a) in 73.6% and 12.4% yield, respectively. Pure products (7a and 8a) were separated by preparative TLC. 1α-ol (8a); IR: 1750, 3530; NMR δ: 1.84 (d, J=1.5 Hz, 4-CH_3), 3.40 (t, J=3 Hz, 1-H), 5.25 (bs, 3-H).

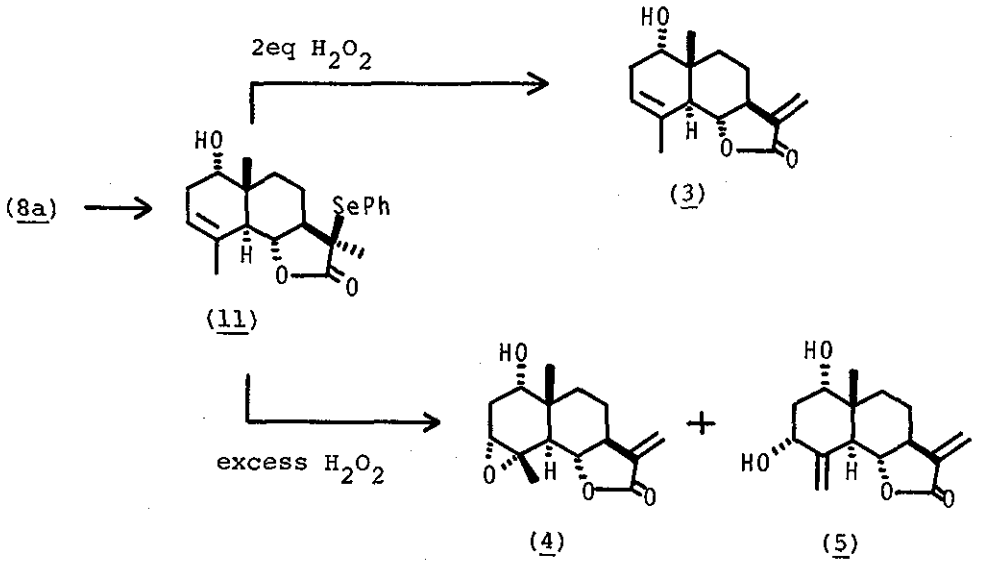
Phenylselenenylation of 1α-ol (8a), according to the procedure described by Grieco *et al.*,[8] gave a phenylselenide (11) as an oil [NMR δ: 1.52 (s, 11-CH_3)]. Oxidation of the selenide (11) with 2 molar equivalents of 30% H_2O_2 in THF-AcOH at 0°C produced a selenoxide as an intermediate which underwent facile *syn*-elimination to give an *exo*-methylene compound (3), mp 116-118° [Mass *m/e*: 248, M^+; $[\alpha]_D^{23°}$ +153°; NMR δ: 0.80 (s, 10-CH_3), 1.83 (bs, 4-CH_3), 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 $\prec^{H}_{H}$)]. 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.[9,10]

On the other hand, oxidation of 11 with an excess (ca. 20 molar eq.) of 30% H_2O_2 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^+, 249 $(M-15)^+$, 246 $(M-18)^+$, 231 $(M-15-18)^+$; $[\alpha]_D^{23°}$ +113° ($CHCl_3$); NMR δ: 0.84 (s, 10-CH_3), 1.47 (s, 4-CH_3), 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, $=\!\!<^{H}_{H}$); IR ν_{max}^{KBr} cm^{-1}: 3570, 1755, 1670. Compound (5): mass *m/e*: 264, M^+, 246 $(M-18)^+$; $[\alpha]_D^{23°}$ +108° ($CHCl_3$); NMR δ: 0.78 (s, 10-CH_3), 3.40 (m, 1-H), 3.98 (t, *J*=11 Hz, 6-H), 4.38 (t, $W_{1/2}$ =8 Hz, 3-H), 5.02, 5.13 (bs, 4- $=\!\!<^{H}_{H}$), 5.36, 6.03 (d, *J*=3 Hz, 11- $=\!\!<^{H}_{H}$); IR ν_{max}^{KBr} cm^{-1}: 3300, 1770, 1755, 1650].

Grieco *et al.*[11] recently reported a similar fact that treatment of the phenylselenide of saussurea lactone with 2 equivalents of 30% H_2O_2 gave dehydrosaussurea lactone, whereas with a large amount of 30% H_2O_2 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:[12] mp 215°, $[\alpha]_D$ +128°), and NMR spectrum[10]) and ludovicin B (reported:[12] mp 152°, $[\alpha]_D$ +138°), respectively, which had been isolated from *Artemisia ludoviciana* subsp. *mexicana* by Lee and Geissman.[12]



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** Present address: Shin Nihon Jitsugyo Co. Ltd., Tokyo Research Laboratory.

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