Tetrahedron Letters No. 47, pp 4137 - 4140, 1975. Pergamon Press. Printed in Great Britain.

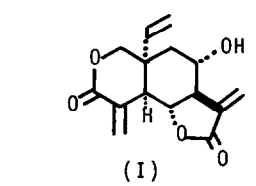
CHEMICAL TRANSFORMATION OF α-SANTONIN INTO SESQUITERPENE α-METHYLENE-γ-LACTONES, ARGLANINE AND SANTAMARINE.[1]

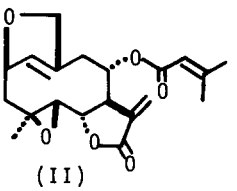
Koji Yamakawa,* Tomohiro Tominaga,** and Kiyoshi Nishitani
Faculty of Pharmaceutical Sciences, Science University of Tokyo
Ichigaya-funagawara-machi, Shinjuku-ku, Tokyo 162, Japan

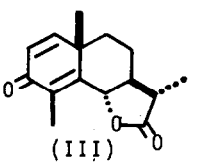
(Received in Japan 5 September 1975; received in UK for publication 6 October 1975)

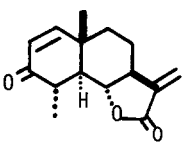
Study on sesquiterpene α-methylene-γ-lactones has been due in large part to interest in several biologically active natural products.[2] Vernolepin (I) and elephantin (II), novel sesquiterpene tumor inhibitor, have the α-methylene-γ-lactone moiety as a major structural feature. Recently, there has been an increasingly large amount of research devoted to developing synthetic routes to α-methylene-γ-lactones.[3]

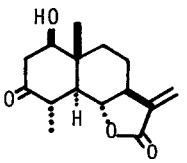
In a previous paper we reported[4] the chemical transformation of α-santonin (III) into sesquiterpene α-methylene-γ-lactones, tuberiferine (IV) and artecalin (V). In this communication we will report a stereoselective transformation of α-santonin (III) into arglanine (VI)[5] and santamarine (VII)[6] which possess an α-methylene-γ-lactone structural feature.

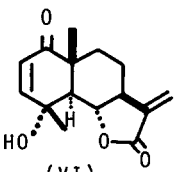

(I)

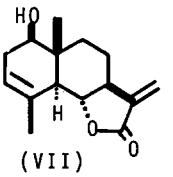

(II)


(III)


(IV)

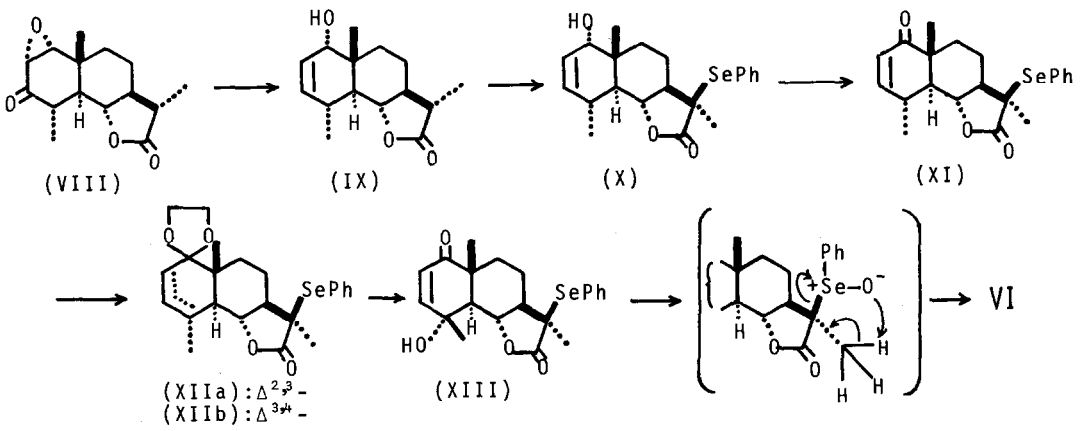

(V)


(VI)


(VII)

Chemical Transformation of α-Santonin into Arglanine

α-Epoxyketone (VIII)[7] was prepared from Δ^1-α-tetrahydrosantonin by the action of 30% H_2O_2 in alkaline solution. A solution of VIII in ethanol containing acetic acid and 85% hydrazine hydrate was warmed at 30-40°, N_2 was evolved and allyl alcohol (IX), mp 141-143° [m/e 250, M^+; ν_{OH} 3600, $\nu_{C=C}$ 1645; NMR δ: 3.42 (d, J=5 Hz; 1-H), 5.56-5.90 (m; H⟩⟨H)] was produced in 22.4-33.7% yield. Phenylselenenylation of IX by Grieco's procedure[8] afforded phenylselenide (X), mp 139-140.5° [m/e 406, M^+; NMR δ: 1.51 (s; 11-Me)] in 90% yield. Oxidation of X with active MnO_2 gave enone (XI), viscous oil. Ketalization of XI with ethylene glycol in the presence of p-toluenesulfonic acid in benzene afforded a mixture of double bond isomeric ketals (XIIa and XIIb) and the separation of the ketals was unsuccessful. Deketalization of a mixture of ketals (XIIa and XIIb) under several conditions afforded enone (XI) and hydroxy-enone (XIII), mp 154-157° [m/e 420, M^+; ν_{OH} 3540, ν_{CO} 1660; NMR δ: 1.41 (s; 11-Me), 1.55 (s; 4-Me)] whose formation must be due to air oxidation. Hydroxy-enone (XIII) was formed in good yield when O_2 was bubbled into the reaction mixture, but this reaction carried out under an atmosphere of N_2 to give only XI.

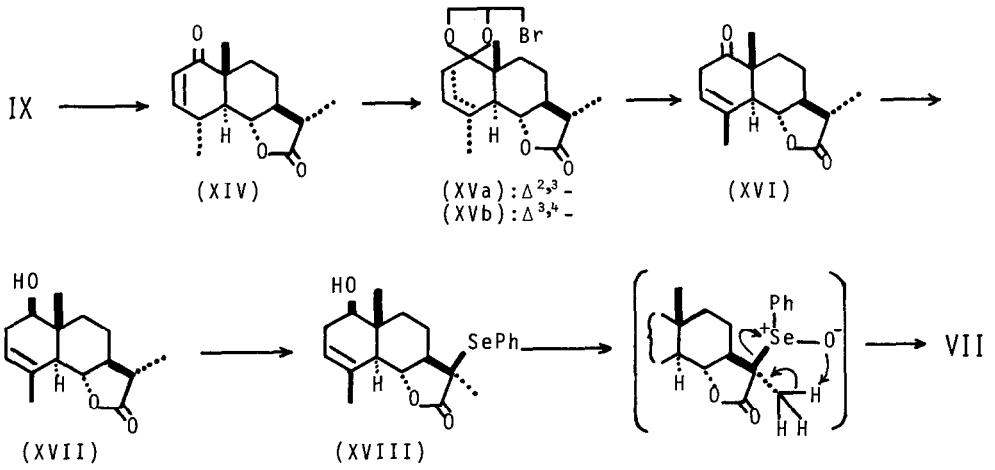


Oxidation of XIII with 30% H_2O_2 in THF-CH_3COOH at 0° formed a selenoxide as an intermediate which underwent facil syn-elimination to give exo-methylene compound (VI), mp 197-201° [m/e 262, M^+; $[\alpha]_D$ 108°; ν_{OH} 3740, ν_{CO} 1745 and 1670; NMR δ: 1.20 (s; 10-Me), 1.55 (s; 4-Me), 4.13 (t, J=11.5 Hz; 6-H), 5.52 and 6.16

(d each, J=3 Hz; )]. Compound VI was identified by comparing its IR and NMR spectrum with that of natural arglanine which was isolated from Artemisia douglasiana Bess by Matueda and Geissman.[5]

Chemical Transformation of α-Santonin into Santamarine

We next report the successful conversion of α-santonin (III) into santamarine (VII) which was isolated from Chrysantenum partenium.[6] Oxidation of en-ol (IX), as an intermediate described above for arglanine, with Jones reagent afforded enone (XIV), mp 112-113.5° [m/e 248, M^+; ν_{CO} 1670; NMR δ: 5.89 and 6.62 (dd each, J=10, 2.5 Hz; )].



In order to shift of the double bond from 2,3- to 3,4-position, ketalization of XIV with bromoglycol, according to Corey's procedure,[9] gave a mixture of isomeric bromo-ketals (XVa and XVb), oil, which were deketalized without separation with zinc in methanol at refluxing for 18 hr. The deketalization products were separated by preparative tlc to give enone (XVI), mp 133-135° (37% yield) [m/e 248, M^+; ν_{CO} 1710; NMR δ: 1.90 (broad s; 4-Me), 5.56 (broad s; 3-H)] and XIV (34% yield). Reduction of XVI with $NaBH_4$ in methanol at 0° for 30 min afforded predominantly 1β-ol (XVII), mp 135.5-137° [m/e 250, M^+; ν_{OH} 3525; NMR δ: 3.63 (dd, J=10, 6.5 Hz; 1-H)]. The IR and NMR spectrum of XVII was in good agreement with that of the reduction product of natural santamarine.[6]

Phenylselenenylation of XVII by Grieco's procedure[8] as desbribed above gave phenylselenide (XVIII), oil [m/e 406, M^+; NMR δ: 1.46 (s; 11-Me)]. Oxidative syn-elimination of XVIII produced a selenoxide as an intermediate which immediately converted to the objective exo-methylene compound (VII), mp 141.5-142.5° in good yield. Compound VII showed an M^+ at m/e 248 in MS spectrum, and absorption bands at 3380 cm^{-1} for OH and 1665 cm^{-1} for C=C stretching vibration in IR spectrum, and signals at δ 0.85 (s; 10-Me), 1.78 (s; 4-Me), 5.37 and 6.04 (), and 5.35 () in NMR spectrum. These spectral data of VII were identical with those of the natural santamarine isolated from Chrysantenum parthenium by Romo de Vivar and Jimenez.[6]

Acknowledgment We thank Professor Matueda, Hirosaki University of Japan, (arglanine) and Professor Romo de Vivar, Universidad Nacional Autinoma de Mexico (santamarine) for IR and NMR spectra.

References and Notes

1. Studies on Terpenoids and Related Alicyclic Compounds Part VI.
2. S.M. Kupchan, M.A. Eakin, and A.M. Thomas, J. Med. Chem., 14, 1147 (1971); K.-H. Lee, E.S. Huang, C. Piantadosi, J.S. Pagano, and T.A. Geissman, Cancer Res. 31, 1649 (1971).
3. For synthetic reviews see (a) P.A. Grieco, Synthesis, 67 (1975); (b) R.B. Gammill, C.A. Wilson, and T.A. Bryson, Synthetic Commun., 5, 245 (1975).
4. Part V of this series, K. Yamakawa, K. Nishitani, and T. Tominaga, Tetrahedron Letters, No. 33, 2829 (1975).
5. S. Matueda and T.A. Geissman, Tetrahedron Letters, 2013 (1967).
6. A. Romo de Vivar and H. Jimenez, Tetrahedron, 21, 1273 (1966).
7. V.K. Honward, E. Siscovic, and A.S. Rao, Tetrahedron, 23, 1273 (1966).
8. P.A. Grieco and M. Miyashita, J. Org. Chem., 39, 120 (1974).
9. E.J. Corey and R.A. Ruden, J. Org. Chem., 38, 834 (1973).

** Research Institute, Nippon Chemiphar Co. Ltd., Misato-City, Saitama 341.