CHEMICAL TRANSFORMATION OF α-SANTONIN INTO BALCHANIN, COLARTIN, AND ARBUSCULIN A, B, C, AND E[1,*]

Koji Yamakawa,* Kiyoshi Nishitani, and Kazutoyo Azusawa

Faculty of Pharmaceutical Sciences, Science University of Tokyo
Ichigaya-funagawara-machi, Shinjuku-ku, Tokyo 162, Japan

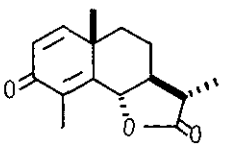
Some sesquiterpene α-methylene-γ-lactones are worthy of attention for their biological activities. The chemical transformation of santonin into sesquiterpene α-methylene-γ-lactones, balchanin, arbusculin A, B, C, and E, and their precursor, colartin, is described.

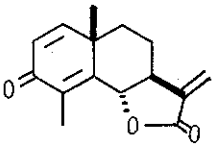
In the previous papers, we reported the chemical transformation of α-santonin (1) into sesquiterpene α-methylene-γ-lactones, tuberiferine,[2] artecalin,[2] argulanine,[3] santamarine,[3] and further into 11-dehydrosantonin[4] (2), mp 154-154.5°, and 11-dehydro-3-oxo-5α-santanolide[4] (3), mp 167-169° (decomp). Studies on some sesquiterpene α-methylene-γ-lactones have been undertaken largely for interest in their biological activities *in vitro* and *in vivo*, and also for the anti-inflammatory activity of tuberiferine, 11-dehydrosantonin (2), and 11-dehydro-3-oxo-5α-santanolide (3).

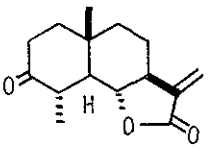
---

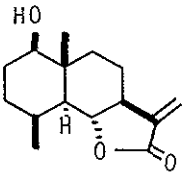
* *Dedicated to Professor S. Sugasawa on the anniversary of his 80th birthday.*

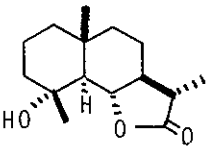
We now wish to report the chemical transformation of α-santonin (1) into balchanin (4), colartin (5), and arbusculin A, B, C, and E (6, 7, 8, and 9).

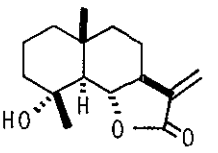

(1)

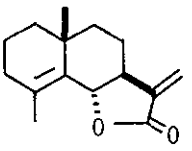

(2)

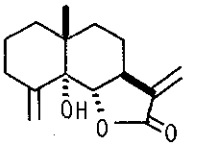

(3)

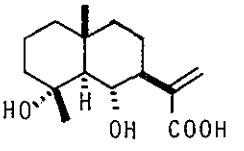

(4)


(5)


(6)


(7)

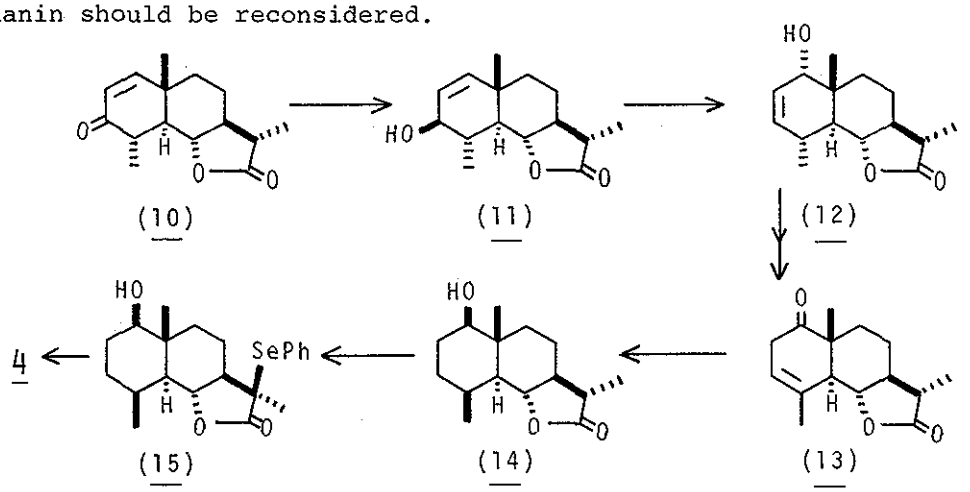

(8)


(9)

Chemical Transformation of α-Santonin into Balchanin

Conversion of the enone[5] (10) into 1α-hydroxy-2-ene[3] (12) was carried out *via* the α-epoxyketone but its yield (22-23%) was unsatisfactory, and preparation of the allylic alcohol (12) was improved. Reduction of 10 with $LiAlH_4$ in THF gave 3β-hydroxy-1-ene[6] (11). A solution of 11 in dioxane containing 1N H_2SO_4 was refluxed for 8 hr to give 12 in 67% yield, together with the starting material in 14% yield. Conversion of 12 into 1-oxo-3-ene (13) was already reported by us.[3] Catalytic reduction of 13 with PtO_2 in EtOH gave 4β-methyl-1β-ol (14) or dihydrobalchanin, mp 166-167°,

$[\alpha]_D^{25°}$ +43° (reported[7,8] mp 164-166°, $[\alpha]_D$ +34°) [MS *m/e*: 252 (M^+); IR cm^{-1}: 3480, 1780; NMR δ: 1.04 (d, *J*=7 Hz, 4-Me), 1.07 (s, 10-Me), 1.24 (d, *J*=7 Hz, 11-Me), 3.35 (m, 1-H), 4.05 (m, 6-H)] which showed identical IR and NMR spectra as that of authentic dehydrobalchanin.[7,8] Phenylselenenylation of 14 by Grieco's procedure[9] gave phenylselenide (15) as an oil [NMR δ: 1.46 (s, 11-Me)]. Oxidation of 15 produced selenoxide as an intermediate which immediately converted to the objective oxo-methylene compound (4), "(+)-balchanin" mp 136-138°, $[\alpha]_D^{23°}$ +68.0°, in a good yield. [MS *m/e*: 250 (M^+); IR cm^{-1}: 3610 (OH), 1760 (CO), 1665 (C=C); NMR δ: 1.00 (s, 10-Me), 1.00 (d, *J*=7 Hz, 4-Me), 3.35 (m, 1-H), 4.00 (t, *J*=10 Hz, 6-H), 5.35, and 6.00 (1H each, d, *J*=3 Hz, $\prec^{H}_{H}$)]. The stereoformula of 4 was confirmed to be 1β-hydroxy-4,5α(H)-11-dehydrosantanolide from the synthetic route and these spectral data. Suchy[10] reported isolation of balchanin (mp 142°; $[\alpha]_D^{20°}$ +96.6°) from *Artemisia balchanorum*, and assigned 4 as its structure. However, 4 and balchanin do not agree in their physical constants.[11] Thus, the structure of balchanin should be reconsidered.

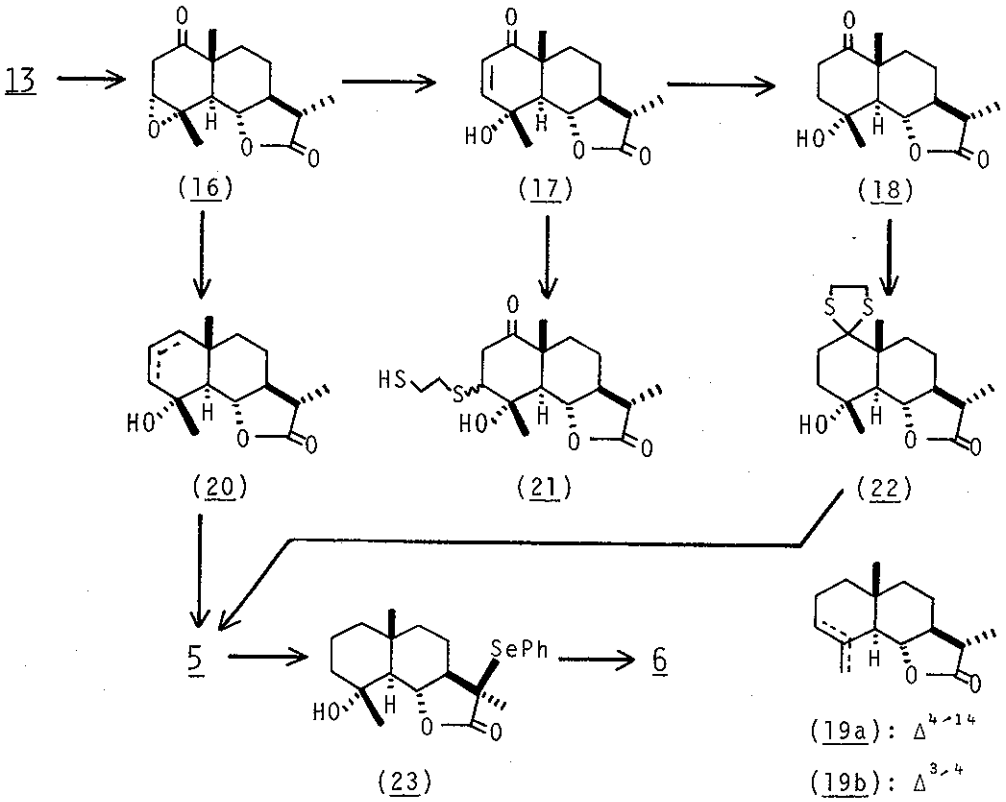


Chemical Transformation of α-Santonin into Colartin, and Arbusculin A, B, and E

Treatment of 1-oxo-3-ene (13) with *m*-chloroperbenzoic acid in $CHCl_3$ stereoselectively gave α-epoxide (16), mp 146-147° (reported[7] mp 154-156°) in 71% yield. 16 was adsorbed on silica gel, allowed to stand at room temperature for 3 days and its elution with EtOAc gave 17 quantitatively, whose physical and spectral data agreed with those of natural vulgarin.[7] Some reactions were attempted in order to reduce the 1-oxo group in 16, 17, and 18 into a methylene group. The Wolff-Kishner reduction of vulgarin (17) and the Clemmensen reduction of dihydrovulgarin[12] (18), mp 175-176°, both gave a complex mixture. The Wolff-Kishner reduction of 18 gave a mixture of olefins, 19a [NMR δ: 4.74, 4.90 (1H each, 14-H)] and 19b [NMR δ: 5.35 (3-H)] in 15% total yield in 2:1 ratio as evidenced by NMR analysis. On the other hand, the Wolff-Kishner reduction of the epoxyketone (16) gave 4α-hydroxy-1(or 2)-ene (20), mp 93-95° in 8.3% yield. [MS *m/e*: 250, (M^+); IR cm^{-1}: 3620, 1780; NMR δ: 5.42 (2H, bs, vinylic H)], which was reduced with 10% Pd-C in EtOAc to give 5, colartin, mp 108-110°, $[\alpha]_D^{21°}$ +12.9° (reported[12] mp 107-108°; $[\alpha]_D^{21°}$ +11.4°) [MS *m/e*: 252 (M^+), 237 $[M-15]^+$, 234 $[M-18]^+$, 219 $[M-33]^+$; IR cm^{-1}: 3620, 1780; NMR δ: 0.97 (s, 10-Me), 1.22 (d, *J*=7Hz, 11-Me), 1.32 (s, 4-Me), 1.68 (d, *J*=11 Hz, 5-H), 3.00 (OH), 4.05 (dd, *J*=11, 9 Hz, 6-H)]. The physical and spectral data of 5 were in good agreement with those of natural colartin isolated from *Artemisia tripartita ssp rupicola* by Irwin and Grissman.[13]

In order to improve the yield of 5, some reaction were attempted. Thioketalization of 17 gave an unexpected ethanedithiol adduct (21),

mp 158-159° [MS *m/e*: 358 (M^+), 265 $[M-93]^+$; IR cm^{-1}: 3500, 1780, 1710] in 46.6% yield together with the starting ketone (17) in 21% yield. Treatment of 18 with ethanedithiol in AcOH containing *p*-toluenesulfonic acid at room temperature for 9 days gave a thioketal (22), mp 219-220° [MS *m/e*: 342 (M^+); IR cm^{-1}: 3590, 1790] in 72% yield. Reductive desulfurization of 22 with Raney nickel in acetone gave colartin (5) in 65% yield (46.8% overall yield from 16).



Phenylelenenylation of 5 by Grieco's method[9] gave phenylselenide (23), mp 164-167° [NMR δ: 1.52 (s, 11-Me)] which was treated with H_2O_2-AcOH in THF to give 6, arbusculin A, mp 78-79.5° $[\alpha]_D^{23°}$ +25.0° (reported[12] mp 76.5-77.5°; $[\alpha]_D^{24°}$ +25.8°) [MS *m/e*: 250 (M^+), 235

$[M-15]^+$, 232 $[M-18]^+$, 217 $[M-33]^+$; IR cm^{-1}: 3585, 1765, 1662; NMR δ: 0.99 (s, 10-Me), 1.31 (s, 4-Me), 1.81 (d, J=11.5 Hz, 5-H), 2.58 (m, 7-H), 3.25 (OH), 4.05 (t, J=11 Hz, 6-H), 5.46 and 6.08 (1H each, d, J=3 Hz, $=\!\!<^{H}_{H}$)]. These spectral data of 6 agreed with those of arbusculin A which was isolated from *Artemisia arbuscula* by Irwin and Geissman.[13]

Irwin and Geissman have already reported the conversion of arbusculin A (6) into arbusculin B[13] (7), arbusculin C[14] (8), and arbusculin E[14] (9). Therefore, the chemical transformations of α-santonin (1) into arbusculin B, C, and E (7, 8, and 9) were tentatively achieved.

REFERENCES AND NOTES

1 Studies on Terpenoids and Related Alicyclic Compounds XI. Part X. K. Yamakawa and T. Satoh, Chem. Pharm Bull (Tokyo), 1977, 25 in press.
2 K. Yamakawa, K. Nishitani, and T. Tominaga, Tetrahedron Lett., 1975, 2829.
3 K. Yamakawa, T. Tominaga, and K. Nishitani, Tetrahedron Lett., 1975, 4137.
4 K. Yamakawa and T. Tominaga, Jpn Patent Appl. July 14, 1976.
5 E.J. Corey and A.G. Hortman, J. Am. Chem. Soc., 1965, 87, 5736.
6 K. Yamakawa and K. Nishitani, Chem. Pharm. Bull. (Tokyo), 1976, 24, 2810.
7 H. Yoshioka, W. Renold, N.H. Fischer, A. Higo, and T.J. Mabry, Phytochemistry, 1970, 9, 823.
8 A. Romo de Vivar and H. Jimenez, Tetrahedron, 1965, 21, 1741.
9 P.A. Grieco and M. Miyashita, J. Org. Chem., 1974, 39, 120.
10 M. Suchy, Coll. Czech. Chem. Commun., 1962, 27, 2925.
11 The authors thank Prof. Herout for a copy of IR spectrum of balchanin.
12 T.A. Geissman and G.A. Ellestad, J. Org. Chem., 1962, 27, 1855.
13 M.A. Irwin and T.A. Geissman, Phytochemistry, 1969, 8, 2411.
14 M.A. Irwin and T.A. Geissman, Phytochemistry, 1971, 10, 637.

Received, 18th May, 1977