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

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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).

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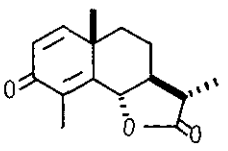
* *Dedicated to Professor S. Sugasawa on the anniversary of his 80th birthday.*

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).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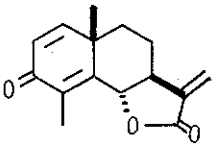
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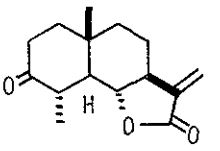
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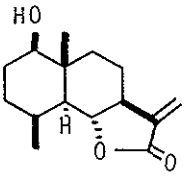
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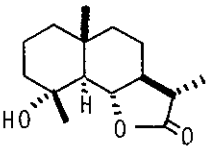
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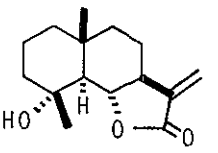
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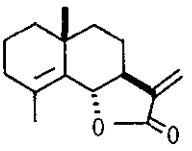
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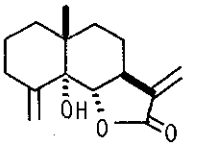
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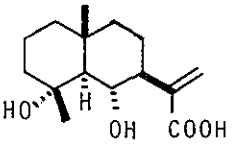
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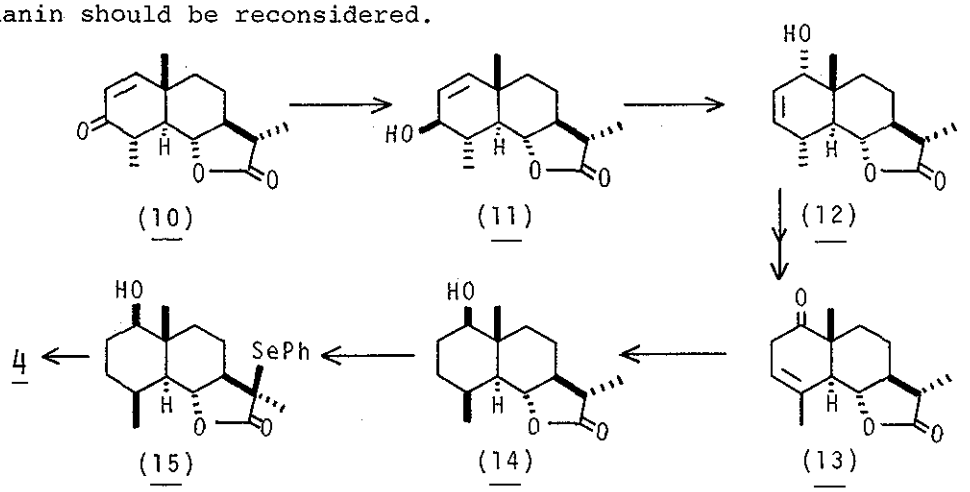
Chemical Transformation of α-Santonin into Balchanin

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.

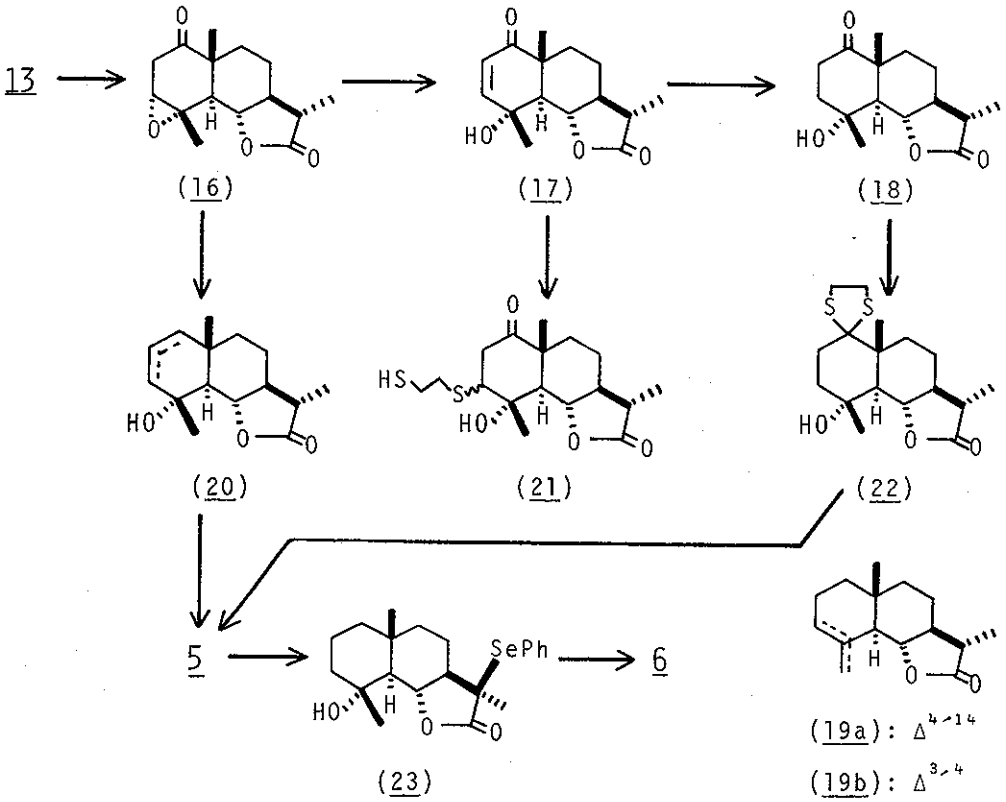


Chemical Transformation of α-Santonin into Colartin, and Arbusculin A, B, and E

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 $\delta$: 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.

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Received, 18th May, 1977