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SYNTHETIC STUDIES OF WITHANOLIDE I
SYNTHESIS OF AB RING MOIETY OF WITHAFERIN A

Masaji Ishiguro, Akira Kajikawa, Toshio Haruyama,
Masuo Morisaki and Nobuo Ikekawa*

Laboratory of Chemistry for Natural Products
Tokyo Institute of Technology, Meguro-ku, Tokyo, Japan

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Withanolide is a new series of naturally occuring C_{28} steroidal lactones[1]. Among those, withaferin A (1)[2] has been paid a special attention for its tumor-inhibitory activity. Structural features of 1 are the epoxide and quinoid-like moiety in AB ring, as well as the unsaturated lactone in the side chain. These functionality has been shown to be important for the tumor-inhibitory activity of several class of terpenoids[3]. We report herein a stereoselective synthesis of 5β,6β-epoxy-1-oxo-cholest-2-en-4β-ol(2) as a model compound of 1. It is noteworthy that 2 has an inhibitory effect against the growth of Sarcoma 180 ascites tumor.

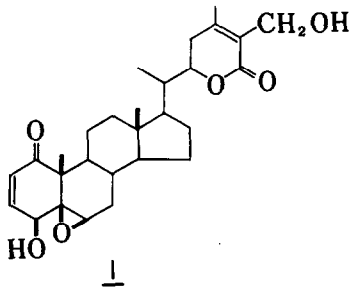
1α,2α-Epoxy-3-oxo-5α-cholestan-6β-ol acetate(3)[4] was converted to the conjugated ketone 4, mp 94-94.5°, by reduction with hydrazine, followed by oxidation with Jone's reagent. Hydrolysis of 4 and the subsequent dehydration with $POCl_3$-pyridine gave the dienone 5 (45 % from 3), mp 98.5-100°. More conveniently, 5 was prepared (55 %) from 1α-hydroxycholesterol(6)[5] by the following sequence : 1) a partial acetylation with Ac_2O-AcOH affording 1α-hydroxy-3β-acetate; 2) Jone's oxidation; and 3) treatment with NaOH in aqueous dioxane.

Reaction of 5 with m-chloroperbenzoic acid afforded 5α,6α-epoxide 7[6] (69 %), mp 123-124° and 5β,6β-epoxide 8[7] (25 %), mp 113-115°. The undesired 8 was transformed into 7 by the treatment with $HClO_4$-THF giving the glycol 9a[8], mp 141.5-

143.5°, and the subsequent reaction of its mesylate 9b with $NaHCO_3$-pyridine. Thus, 7 was secured in a over all yield of 82 % from 5. Those chemical transformation, e.g. 8 → 9a → 9b → 7 , also afforded a further proof for configurational assignments of 7 and 8 based on nmr data.

A base-catalyzed rearrangement of 7 (NaOH-dioxane-H_2O, reflux, 4 hr) gave the hydroxydienone 10a[9] (97 %), mp 156-157°. Stereoselective introduction[10] of 4β,5β-diol function was effected by oxidation of acetate 10b or mesylate 10c[12] with OsO_4 affording the glycol 11a[11] , mp 171-172° and 11b, respectively.

The mesylate 11b was treated with NaOH-pyridine (70°, 10 min) to give the final compound 2 (85 % from 10a), mp 220.5-223.5°, $[\alpha]_D$ +39° (c, 0.16, $CHCl_3$), m/e 414.3128 (M^+ requires 414.3134), nmr δ($CDCl_3$), 0.65 (3H, s, C-18-Me), 1.40



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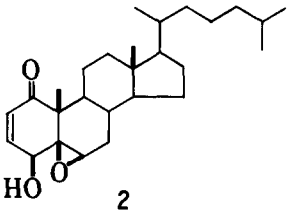

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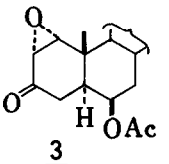

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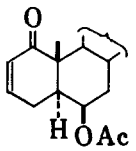

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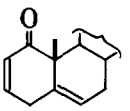

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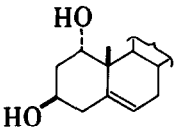

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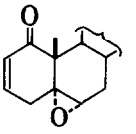

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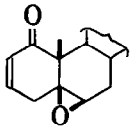

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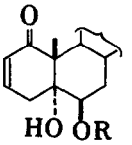
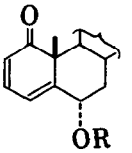
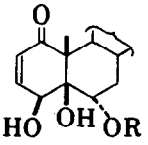


9a, R=H
9b, R=Ms



10a, R=H
10b, R=Ac
10c, R=Ms



11a, R=Ac
11b, R=Ms

(3H, s, C-19-Me), 3.20(1H, bs, $W_{\frac{1}{2}}$ = 5 Hz, C-6-H), 3.74 (1H, d, J = 6 Hz, C-4-H), 6.20 (1H, d, J = 10 Hz, C-2-H) and 6.93 ppm (1H, dd, J = 10 and 6 Hz, C-3-H). The structure of 2 was further corroborated with the perfect agreement of its relevant nmr signals with those of 1[13].

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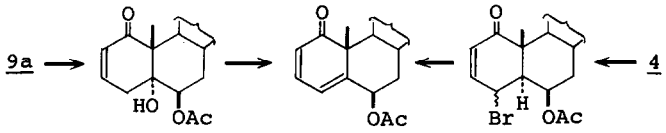
6. 7, nmr δ($CDCl_3$), 1.30 (3H, s, 19-Me), 2.98 (1H, d, J = 5 Hz, C-6-H), 3.07 (1H, dt, J = 18 and 2 Hz, C-4-H), 5.95 (1H, dd, J = 10 and 2 Hz, C-2-H), and 6.65 ppm (1H, dq, J = 10, 5 and 2 Hz, C-3-H).

7. 8, nmr δ($CDCl_3$), 1.23 (3H, s, 19-Me), 2.95 (1H, dt, J = 21 and 2 Hz, C-4-H), 3.10 (1H, bs, $W_{\frac{1}{2}}$ = 5 Hz, C-6-H), 6.00 (1H, dd, J = 10 and 2 Hz, C-2-H) and 6.81 ppm (1H, dq, J = 10, 5 and 2 Hz, C-3-H).
The ratio of α- to β-epoxide (3 : 1) contrasts markedly by the results of Glotter et al that β-epoxide was the major product of epoxidation of withanolide L and related compounds containing 1-oxo-2,5,14-triene system : E. Glotter, A.Abraham and D.Lavie, Tetrahedron, 29, 1353(1973).

8. 9a, nmr δ($CDCl_3$), 1.32 (3H, s, 19-Me), 3.30 (1H, dt, J = 20 and 2 Hz, C-4-H), 3.65 (1H, bs, $W_{\frac{1}{2}}$ = 5 Hz, C-6-H), 5.88 (1H, dd, J = 10 and 2 Hz, C-2-H) and 6.60 ppm (1H, dq, J = 10, 5 and 2 Hz, C-3-H).
The same glycol, 9a was obtained from 7 by a similar acid treatment. The glycol 9a was further transformed by acetylation followed by dehydration ($SOCl_2$-pyridine) into 1-oxo-cholesta-2,4-dien-6β-ol acetate, mp 103.5-105°,

whose configuration at C-6 (and therefore, of 9a and 8) was firmly established as β, by an alternative synthesis from 4 by bromination (NBS-CCl_4), followed by dehydrobromination ($CaCO_3$-DMA).



9. 10a, nmr δ($CDCl_3$), 1.23 (3H, s, 19-Me), 4.53 (1H, m, C-6-H), 6.00 (1H, d, J = 10 Hz, C-2-H), 6.37 (1H, d, J = 6 Hz, C-4-H), and 7.03 ppm (1H, dd, J = 10 and 6 Hz, C-3-H).

10. A similar stereoselectivity (4β,5β-attack) was observed with epoxidation with m-chloroperbenzoic acid of 1-oxo-cholesta-2,4-diene and 1-oxo-cholesta-2,4-dien-6β-ol.

11. 11a, nmr δ($CDCl_3$), 1.26 (3H, s, 19-Me), 5.06 (1H, bs, $W_{\frac{1}{2}}$ = 6 Hz, C-4-H), 5.20 (1H, m, C-6-H), 6.00 (1H, dd, J = 10 and 2 Hz, C-2-H) and 6.53 ppm (1H, dd, J = 10 and 2 Hz, C-3-H), $\Delta_{CDCl_3-C_6D_6}$ = -0.14 ppm (shift of 19-Me).

12. Mesylate 10c was rather unstable and easily converted to 1-oxo-cholesta-2,4,6-triene (λ_{max} 355 nm) by allowing to stand over room temperature for a few hours.

13. We thank Professor S.M.Kupchan for sending us nmr spectrum of withaferin A.