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Facile conversion of 23-hydroxyspirosolane into pregnane

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Abstract—Two novel reactions with regard to steroidal alkaloid sapogenols obtained from ripe tomato have been found. These reactions have been attained by simple facile method in only refluxing with pyridine and water. One is isomerization of a spirosolane derivative, isoesculeogenin A (**2**), into a rare solanocapsine derivative, esculeogenin B (**3**), disclosing a chemical correlation between isoesculeogenin A and esculeogenin B. Another is conversion of a 23-hydroxyspirosolane derivative, esculeogenin A (**1**), into a pregnane derivative (**4**), presenting an epoch-making method for derivation of steroidal hormone material.
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Recently, we obtained major novel steroidal alkaloid glycosides, named esculeoside A[1] and esculeoside B,[1] from the pink color type and the red color type, respectively, of the ripe tomato (*Lycopersicon esculentum* MILL.) fruits for the first time. On the way to clarify the structures of their novel sapogenols, esculeogenin A (**1**),[1] the sapogenol of esculeoside A, isoesculeogenin A (**2**), [2] the sapogenol of lycoperoside F,[3] and esculeogenin B (**3**),[2] the sapogenol of esculeoside B, we have found novel reactions, isomerization of isoesculeogenin A (**2**) into a rare skeleton of solanocapsine-type steroid,[4] esculeogenin B (**3**), and an excellent conversion of esculeogenin A (**1**) into steroidal hormone, a pregnane derivative (**4**), by simple facile reactions only refluxed with pyridine and water.

The fact that different-type sapogenols were obtained from the pink color type and the red color type is remarkable. Correlation between esculeogenin A (**1**) and esculeogenin B (**3**) was deduced in the preceding paper.[1] Thus, an attempt for changing esculeogenin A (**1**) or/and isoesculeogenin A (**2**) into esculeogenin B (**3**) in order to reveal the chemical correlation between esculeogenin A (**1**) and esculeogenin B (**3**) has resulted in the finding of the following new transformation. That is, isoesculeogenin A (**2**) was refluxed with pyridine–water (2:1) for 3 h. Subsequent separation of the reaction mixture with silica gel provided a major product, which was identical with esculeogenin B (**3**),[5] 22,26-epimino-16β,23-epoxy-3β,23,27-trihydroxy-(5α,22*S*,23*R*,25*S*)-cholestane in a 20.8% yield. The trigger of this reaction was protonation to the C-16–oxygen, followed by ketonization at C-23, to where the C-16–oxygen anion attacked to form a six-membered E-ring as shown in Scheme 1. This reaction is regarded as the first time to interpret a chemical correlation between naturally occurring spirosolane and solanocapsine skeletons.

Meanwhile, esculeogenin A (**1**) was refluxed with pyridine for 3 h, followed by heating with pyridine and water for 2 h in the same reaction to afford a major product (**4**)[6] in a 20.3% yield accompanied by a side-product (**5**) in a 17.8%. Compound **4** was obtained as colorless needles, mp 193–197 °C, $[\alpha]_D$ +67.4° (pyridine), of which structure was confirmed by the ^{1}H NMR and ^{13}C NMR spectroscopy analyses involving ^{1}H–^{1}H COSY, ^{1}H–^{13}C HMQC, and ^{1}H–^{13}C HMBC, and their signals were assigned as follows: three tertiary methyl groups at δ 0.82 (3H, s, H_3-19), 1.43 (3H, s, H_3-18), and 2.33 (3H, s, H_3-21), two oxygen-bearing methine protons at δ 3.86 (1H, m, H-3) and 4.94 (1H, overlapped, H-16) in the ^{1}H NMR spectrum. On the other hand, ^{13}C NMR signals displaying total 21 carbon signals were composed of three methyl groups at δ 12.5 (C-19), 14.7 (C-18), and 30.8 C-21), two oxygen-bearing methine carbons at δ 70.6 (C-3) and 71.8 (C-16), one

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Keywords: *Lycopersicon esculentum*; Tomato steroidal alkaloids sapogenol; Spirosolane; Isomerization; Solanocapsine; Pregnane.

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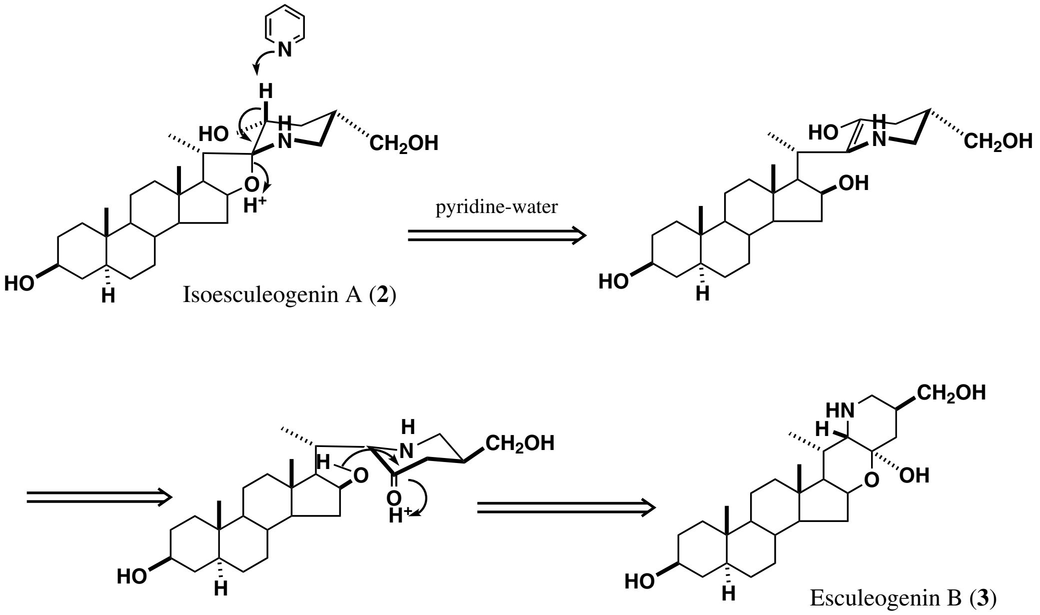
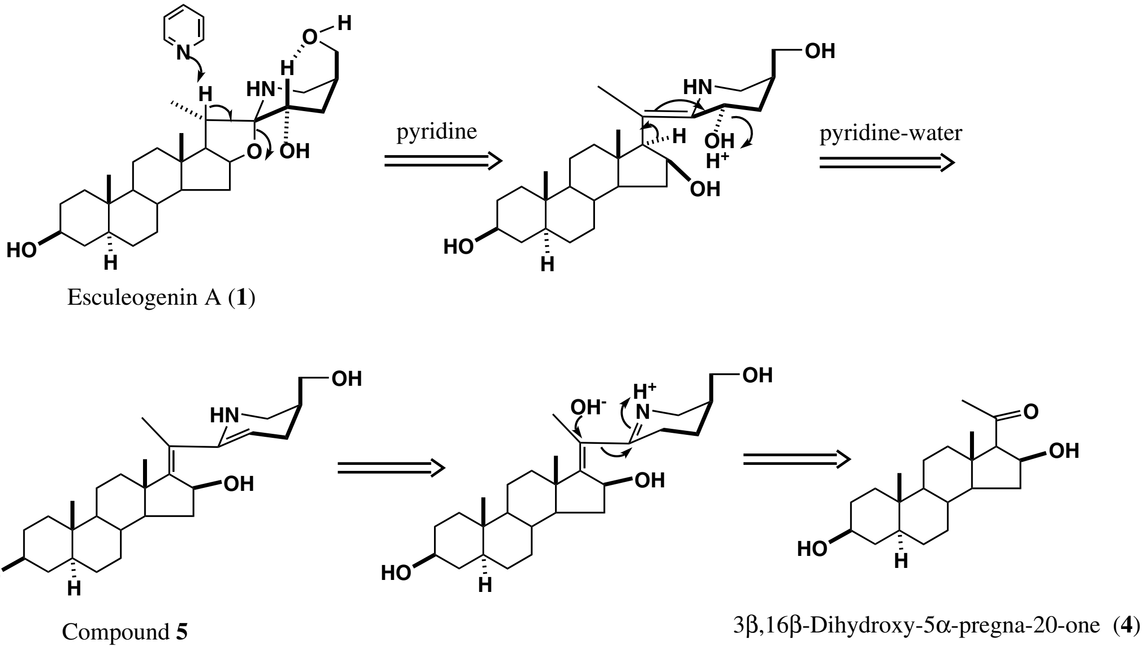


Isoesculeogenin A (**2**)

Esculeogenin B (**3**)

Scheme 1. Isomerization of isoesculeogenin A (**2**) into esculeogenin B (**3**).

carbonyl group at δ 208.5 (C-20), two quaternary carbons at δ 35.9 (C-10) and 42.4 (C-13), five methine carbons at δ 34.9 (C-8), 45.3 (C-5), 54.4 (C-14), 54.9 (C-9), and 69.3 (C-17) and eight methylene carbons at δ 21.0 (C-11), 29.1 (C-6), 32.4 (C-2), 32.5 (C-7), 37.5 (C-1), 38.2 (C-15), 39.0 (C-4), and 39.3 (C-12). Moreover, 2D NOESY was observed between H_3-18 and H_3-21, and between H-16 and H-17, indicating both H-16 and H-17 to be oriented in α. Therefore, compound **4** was determined to be 3β,16β-dihydroxy-5α-pregna-20-one, being identical with lycopersiconol[7] isolated from the tomato stock roots. Compound **5** exhibited the following signals: ^{1}H NMR (pyridine-d_5): δ 0.81 (6H, s, H_3-18, H_3-19), 1.92 (3H, s, H_3-21), 3.83 (1H, m, H-3), 5.21 (1H, m, H-16), 5.68 (1H, d, $J = 3.1$ Hz, H-23), ^{13}C NMR (pyridine-d_5) C-1–27: δ 37.4, 32.3, 70.6, 39.3, 45.3, 29.1, 32.5, 35.2, 54.7, 35.9, 21.0, 40.1, 41.9, 56.4, 32.5, 77.3, 146.3, 12.5, 14.0, 93.5, 25.0, 164.5, 107.9, 32.5, 36.6, 51.1, 64.3, which supported a deduced structure as shown in Scheme 2. Compound **5** was further refluxed with pyridine and water for 2 h to provide compound **4** in a 65% yield, thus suggesting compound **5** to be an intermediate into **4**. The mechanism for this reaction is tentatively speculated as following: acquisition of H-20 by pyridine caused a double-bond formation between C-20 and C-22 and opening of E-ring,



Esculeogenin A (**1**)

Compound **5**

3β,16β-Dihydroxy-5α-pregna-20-one (**4**)

Scheme 2. Conversion of esculeogenin A (**1**) into pregnane derivative (**4**).

followed by dehydration of C-23–OH to form a 22(N)-ene derivative, of which nitrogen was then protonated, and transfer of the 22(N)-ene to the nitrogen raised bond fission between C-20 and C-22 as shown in Scheme 2.

This facile reaction bearing steroidal hormone material in one shot reaction from 23-hydroxyspirosolane derivative would be applied to naturally abundant spirostanol and spirosolane derivatives after 23-hydroxylation. As an admirable novel route for the production of the raw material of steroidal hormone, its practical use is expected.

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2. Fujiwara, Y.; Matsushita, S.; Yoshizaki, N.; Ikeda, T.; Ono, M.; Nohara, T. The Abstract Paper, pp. 257–262 of 46th Symposium on the Chemistry of Natural Products (Hiroshima, 2004). Isoesculeogenin A (**2**): Colorless needles, mp 206–213 °C, positive FABMS: 448 ($C_{27}H_{45}NO_4$, M^++H), ^{1}H NMR (500 MHz, pyridine-d_5): δ 0.80 (3H, s, H_3-19), 0.95 (3H, s, H_3-18), 1.54 (3H, d, J = 6.8 Hz, H_3-21), 3.17, 3.23 (2H, m, H_2-26), 3.72, 3.75 (2H, m, H_2-27), 3.80 (1H, m, H-3), 4.28 (1H, dd, J = 3.0, 10.0 Hz, H-23), 5.29 (1H, m, H-16). ^{13}C NMR (125 MHz, pyridine-d_5), C-1–27: δ 37.5, 32.3, 70.6, 39.2, 45.2, 29.1, 32.6, 35.3, 54.8, 35.9, 21.5, 40.7, 40.1, 56.7, 34.3, 82.7, 63.7, 17.3, 12.5, 44.1, 16.5, 102.5, 72.2, 32.4, 35.3, 45.9, 65.6.
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5. Esculeogenin B (**3**): an amorphous powder, $[\alpha]_D$ −96.2° (c 0.05, pyridine), HREIMS calcd for $C_{27}H_{45}NO_4$ (M^+): 447.3349. Found: 447.3298. ^{1}H NMR spectrum (500 MHz, pyridine-d_5): δ 0.81 (3H, s, H_3-19), 1.01 (3H, s, H_3-18), 1.67 (3H, d, J = 6.5 Hz, H_3-21), 3.02 (1H, dd, J = 3.1, 10.1 Hz, Ha-26), 3.30 (1H, br d, J = 10.1 Hz, Hb-26), 3.73 (2H, d, J = 6.7 Hz, H_2-27), 3.85 (1H, m, H-3), 4.63 (1H, m, H-16). ^{13}C NMR spectrum (125 MHz, pyridine-d_5), C-1–27: δ 37.6, 32.1, 70.6, 39.3, 45.4, 29.1, 32.6, 35.3, 54.8, 35.9, 21.4, 40.7, 42.1, 53.6, 33.8, 70.6, 62.7, 15.4, 12.6, 27.6, 17.8, 63.0, 96.5, 39.3, 25.2, 43.8, 65.4.
6. 3β,16β-Dihydroxy-5α-pregna-20-one (**4**): Colorless needles, mp 193–197 °C, $[\alpha]_D$ +67.4° (c 0.07, pyridine), IR (KBr): $\nu_{\max}$: 3380, 3290, 1670, 1080 cm^{-1}. HREIMS calcd for $C_{21}H_{34}O_3$ (M^+): 334.2508. Found 334.2506. ^{1}H NMR (500 MHz, pyridine-d_5): δ 0.82 (3H, s, H_3-19), 1.43 (3H, s, H_3-18), 2.33 (3H, s, H_3-21), 2.35 (1H, d, J = 7.9 Hz, H-17), 3.86 (1H, m, H-3), 4.94 (1H, m, H-16). ^{13}C NMR (125 MHz, pyridine-d_5), C-1–21: δ 37.5, 32.4, 70.6, 39.0, 45.3, 29.1, 32.5, 34.9, 54.9, 35.9, 21.0, 39.3, 42.4, 54.4, 38.2, 71.8, 69.3, 14.7, 12.5, 208.5, 30.8.
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