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Peculiar side-chain fission of steroidal glycosides

Alaa Mohamed Nafady,[a] Mohamed Ahmed El-Shanawany,[b] Mahmoud Hamed Mohamed,[c]
Hashim Abdel-Halim Hassanean,[b] Xing-Hua Zhu,[a] Tsutomu Yoshihara,[a] Masafumi Okawa,[a]
Tsuyoshi Ikeda[a] and Toshihiro Nohara[a,]*

[a]*Faculty of Pharmaceutical Sciences, Kumamoto University, Oe-honmachi 5-1, Kumamoto 862-0973, Japan*
[b]*Faculty of Pharmacy, Assiut University, Assiut, Egypt*
[c]*Faculty of Pharmacy, Al-Azhar University, Assiut Branch, Assiut, Egypt*

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Abstract—The characteristic novel steroidal glycosides of the 23,26-oxygenated spirostanol-type and 16,22-dicarbonyl cholestanol-type obtained in our laboratory underwent the peculiar reactions of side-chain fission between C-22 and C-23 of the steroidal skeleton by acid or alkaline hydrolysis. These reactions would be applied to the structural determination of these sorts of glycosides and suggest the biogenetic pathway of the occurrence of C-22 lactone-type glycosides. © 2003 Elsevier Science Ltd. All rights reserved.

Our recent study on the constituents of the fruits of *Solanum anguivi* Lam. has resulted in the isolation and structural characterization of characteristic steroidal glycosides such as 23,26-oxygenated spirostane-type: e.g. 3-*O*-[α-L-rhamnopyranosyl-(1→4)]-α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranosyl (β-chacotriosyl) (22*R*,23*S*,25*R*,26*R*)-3β,23,26-trihydroxyspirost-5-ene (anguivioside I, **1**),[1] 22,26-oxygenated furostane-type: 3-*O*-β-chacotriosyl 23,26-epoxy-3β,22,26-trihydroxyfurost-5-ene (anguivioside II, **2**),[2] and 16,22-dicarbonyl cholestane-type: 3-*O*-β-chacotriosyl (23*S*,25*R*,26*S*)-23,26-epoxy-3β,26-dihydroxycholest-5-en-16,22-dione (anguivioside B, **3**).[3] On the way to their structural determination, we found that a peculiar side-chain fission took place between C-22 and C-23 of their steroidal glycosides by simple acid or alkaline treatment. This paper deals with their novel reactions.

Anguivioside I (**1**) was subjected to acid hydrolysis (refluxed with 1N HCl–MeOH for 1 h) to provide a major sapogenol (**4**) in a yield of 65%. It showed a molecular ion peak at m/z 344 corresponding to $C_{22}H_{32}O_3$ in the EI-MS and signals due to steroidal CH_3-18 (s, δ 0.77), CH_3-19 (s, δ 1.03), CH_3-21 (d, $J=7.3$ Hz, δ 1.32), H-3 (m, δ 3.52) and H-6 (br s, δ 5.31) in the ^1H NMR spectrum (pyridine-d_5). A total of 22 ^{13}C NMR signals (pyridine-d_5) was assigned by the aid of ^1H–^1H COSY, HMQC, and HMBC as follows: signals due to δ 37.3, 31.6, 71.7, 38.3, 141.0, 121.0, 31.9, 31.3, 50.2, 36.6, 20.4, 39.9, 41.5, 54.9, 33.2, 82.7, 59.0, 13.8, 19.4, 36.1, 18.0, 181.3 were assigned to C-1–22, respectively. Consequently, the structure of **4** was characterized as 3β,16β-dihydroxypregna-5-ene-20-carboxylic acid 22,16-lactone identical with vespertilin obtained from *S. vespertilio*,[4] as shown in Chart 1.[5] This sapogenol was also derived from anguivioside II (**2**)[2] by the same reaction.[6] The mechanism for production of this lactone sapogenol (**4**),[4] was speculated as illustrated in Chart 1. As the first step, **1** was plausibly conceivable that **1** was transformed into **2**, which subsequently underwent a bond–bond fission between C-22 and C-23 to afford **4**. Many lactone-type sapogenols and glycosides obtained from *S. vespertilio*,[4,7] *S. hispidum*,[8] *S. nodiflorum*,[2] *S. nigrum*,[9] tomato stock root,[10] *Asparagus dumosus*[11] and *Cestrum nocturnum*[12] are already known; however, their biogenesis remained unclarified. They might be biosynthetically derived from the genuine glycosides of 23,26-oxygenated spirostane- or furostane-type such as **1** or **2** through Chart 1 in the plant body.

Anguivioside B (**3**) was treated with alkaline (refluxed with 3% KOH–MeOH for 30 min) to provide a glycoside (**5**) in 73% yield. It showed a quasimolecular ion

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Keywords: steroidal glycoside; 23,26-oxygenated spirostanol; 16,22-dicarbonyl cholestanol; side-chain fission.

* Corresponding author. Tel.: +81-96-371-4380; fax: +81-96-362-7799; e-mail: none@gpo.kumamoto-u.ac.jp

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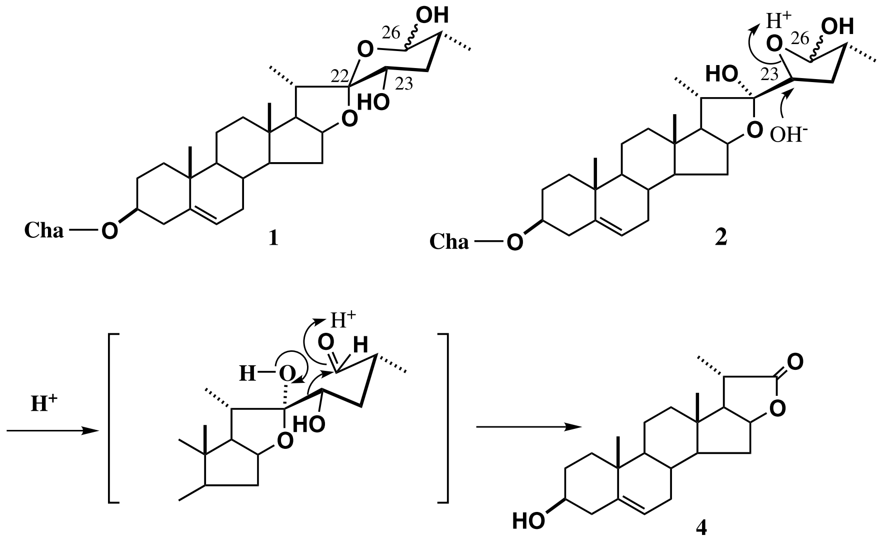

Chart 1. Plausible mechanism for formation of **4**.

peak at m/z 815 $[M+H]^+$ in the positive FABMS. The ^1H NMR spectrum (pyridine-d_5) of **5** exhibited the signals due to CH_3-18 (3H, s, δ 0.72), CH_3-19 (3H, s, δ 1.02), CH_3-21 (3H, d, $J=6.7$ Hz, δ 1.42), H-3 (1H, m, δ 3.83) and H-6 (1H, br d, δ 5.31) together with three anomeric protons (1H, d, $J=7.3$ Hz, δ 5.19, 1H, s, rhamnosyl H-1, δ 6.35 and 1H, s, rhamnosyl H-1, δ 6.35). Signals due to the ^{13}C NMR signals (pyridine-d_5) of **5** displayed a total of 40 carbons, composed of seven methylenes (δ 20.8, 30.0, 32.0, 37.2, 37.9, 38.9, 39.0), four methines (δ 38.7, 50.1, 50.9, 65.4), two quaternary carbons (δ 37.1, 41.9), two olefinic carbons (δ 121.5, 140.9), one oxygen-bearing carbon (δ 78.0), one carbonyl carbon (δ 216.8) and one carboxyl carbon (δ 178.3) together with those of a β-chacotriosyl moiety. Assignments of the ^{13}C NMR signals with the aid of the HMBC spectrum led to the characterization of the structure for **5**, as shown in Chart 2, i.e. 3-*O*-β-chacotriosyl 20-carboxypregna-5-ene-16-one. Production of **5** was estimated as shown in the process of Chart 2.[13]

The reactions of both **1**, **2** and **3** provided C-22 steroids by fission between C-22 and C-23 on the spirostane, furostane and cholestane skeletons in good yield by simple acid or alkaline treatment. These reactions would occur when there is a carbonyl or acetal at C-22, an oxygenated function (hydroxyl or epoxide) at C-23, and a hemiacetal at C-26. These reactions themselves are not only of interest in respect to facile C–C cleavage but also are applicable to the structural determination for these sorts of steroidal glycosides, and they strongly suggest the biogenetic pathway for the occurrence of the lactone-type glycosides of **3**, the biogenesis of which has so far remained as an unsolved problem.

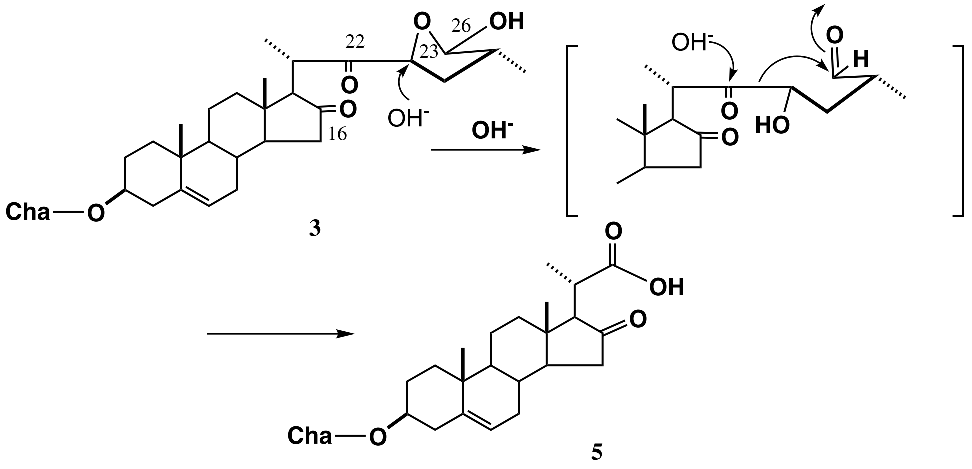

Chart 2. Plausible mechanism for formation of **5**.

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2. ^{13}C NMR (pyridine-d_5): δ 37.5, 30.2, 78.1, 39.0, 140.8, 121.8, 32.3, 31.7, 50.4, 37.2, 21.1, 40.0, 41.1, 56.7, 32.5 (C-1–15), 81.17/81.23 (C-16), 64.0/64.4 (C-17), 16.4/16.6 (C-18), 19.3 (C-19), 38.1 (C-20), 16.25/16.30 (C-21), 109.2/109.9 (C-22), 81.5/84.1 (C-23), 32.6/34.8 (C-24), 38.2 (C-25), 99.2/105.6 (C-26), 13.4/17.3 (C-27), 100.3, 78.7, 77.0, 77.8, 78.0, 61.3 (glc C-1–6), 102.0, 72.6, 72.8, 74.2, 69.5, 18.5 [-glc-(2-1)-rha C-1–6], 102.9, 72.6, 72.8, 73.9, 70.4, 18.7 [-glc-(4-1)-rha C-1–6]. See: Zhu, X.-H.; Tsumagari, H.; Honbu, T.; Ikeda, T.; Ono, M.; Nohara, T. *Symposium Papers of the 43rd Symposium on the Chemistry of Natural Products*, Tokyo, 2001, pp. 335–340.
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13. In the case of the analogous glycoside having sugar A with **3**, it also provided the analogue of **5** in yield 69%; the product: positive FABMS (m/z): 801 $[M+H]^+$; ^{13}C NMR (pyridine-d_5): the signals due to the sapogenol part were superimposable on those of **5**; sugar moiety, δ 100.0, 77.8, 88.2, 77.4, 74.7, 62.4 (inner glc C-1–6), 102.4, 72.5, 72.8, 74.1, 69.6, 18.7 (terminal rha C-1–6), 105.5, 74.7, 77.9, 70.7, 67.3 (terminal xyl C-1–5).