THREE NOVEL CYCLOLANOSTANOL XYLOSIDES FROM CIMICIFUGA RHIZOME

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Three novel xylosides, cimicifugosides H-1(**1**), -3(**2**) and -4(**3**), were isolated from a commercial Cimicifuga Rhizome. Their structures were determined on the basis of chemical and spectrometric evidence including an X-ray crystallographic analysis. The xyloside **1** is 3-*O*-xyloside of (20*R*,24*R*)-24,25-epoxy-3β,11β-dihydroxy-9,19-cyclolanost-7-ene-16,23-dione, while **2** and **3** are 3-*O*-xylosides of 25,26,27-trinor-derivatives from the genin of **1**.

KEYWORDS Cimicifuga Rhizome; cimicifugosides (H-1,3,4); 9,19-cyclolanostanol

Cimicifuga Rhizome (The Pharmacopoeia of Japan, 12th Ed.) is the rhizome of *Cimicifuga simplex* or the other species of the same genus (Ranunculaceae), and has been used as an antipyretic and an antiphlogistic in Chinese medicine. The crude drug available commercially on the Japanese market at present is imported mainly from China. The rhizomes of *Cimicifuga* plants are known to contain many 9,19-cyclolanostane triterpenoids[1] in addition to cinnamic acid derivatives,[2] chromones[3] and indolinones.[4]

During a series of chemical investigation of *Cimicifuga* plants, we isolated three new xylosides, named cimicifugosides H-1 (**1**), $C_{35}H_{52}O_9$, mp 262°C, [5a] H-3 (**2**), $C_{32}H_{48}O_9$, mp 251°C [5b] and H-4 (**3**), $C_{32}H_{48}O_9$, mp 267°C ,[5c] from a batch of Cimicifuga Rhizome purchased on the Japanese market in 1991.

On comparison of the NMR spectral data with those of known *Cimicifuga* xylosides such as 24-*O*-acetyl hydroshengmanol xyloside,[1] it was easily found that the three xylosides are β-D-xylopyranosides of three different triterpenic genins at C-3, and that their genins commonly have a trisubstituted double bond and a cyclopropane ring (partial structure c in Fig.1). But the methylene protons on the cyclopropane ring were observed as a pair of AB doublets at markedly low magnetic field (δ_H 0.96 and 1.96) compared with reported data (δ_H 0.33 and 0.60) on cimigenol xyloside.[1]

Inspection of the ^1H-^1H COSY spectra disclosed that the three xylosides commonly have additional partial structures a, b, d, e and f (Fig.1) in each molecule. When partial structures a to f were applied to the 9,19-cyclolanostane

skeleton, rings A, B, C, and D and a part of the side chain (Chart 1) of the triterpenic genins were presumable except for the binding site (C-11 or 12) of the hydroxyl in the partial structure d. A structure 11β-OH on ring C was presumed as follows : Spatial arrangement of the cyclopropane methylene and the hydroxyl similar to 1,3-diaxially substituted cyclohexane reasonably accounts for the marked downfield shift of the methylene protons.[6]

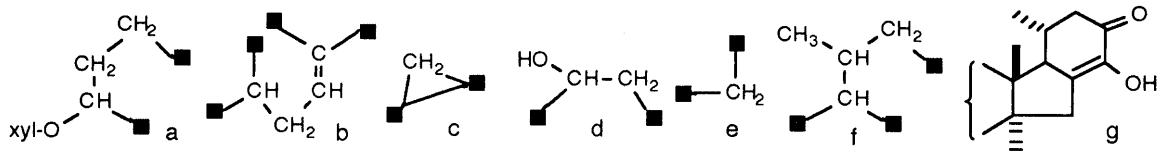
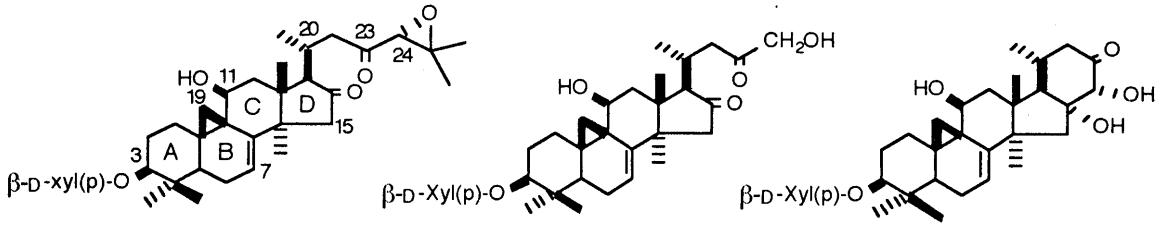


Fig. 1

Cimicifugoside H-1 (**1**) gave a diketonic genin (**4**) on enzymatic hydrolysis. Diacetate of **4** (**5**), $C_{34}H_{48}O_7$, mp 184°C [5d] was subjected to an X-ray crystallographic analysis,[7] and the molecular structure was determined as shown in Fig.2. Cimicifugoside H-1 (**1**) is, then, expressed as (20*R*,24*R*)-24,25-epoxy-11β-hydroxy-3β-(β-D-xylopyranosyloxy)-9,19-cyclolanost-7-ene-16,23-dione.



cimicifugoside H-1(**1**) cimicifugoside H-3(**2**) cimicifugoside H-4(**3**)

Chart 1

Table I. ^{13}C-NMR Chemical Shifts of **1**, **2** and **3** in C_5D_5N

	1	2	3		1	2	3		1	2	3		1	2	3
C-1	27.4	27.4	27.5	16	218.4	218.2	82.0	25	60.7			Xyl.-1	107.4	107.3	107.4
2	29.8	29.7	29.9	17	61.1	61.3	63.6	26	18.4			2	75.5	75.4	75.5
3	88.4	88.4	88.5	18	20.1	20.1	21.2	27	24.6			3	78.5	78.4	78.5
4	40.7	40.7	40.7	19	18.6	18.6	18.8	28	27.7	27.7	28.1	4	71.2	71.1	71.2
5	43.8	43.8	44.2	20	27.6	27.7	25.9	29	25.9	25.9	26.0	5	67.1	67.0	67.0
6	22.1	22.0	22.1	21	20.4	20.3	20.7	30	14.5	14.5	14.6				
7	115.5	115.4	113.8	22	47.4	44.6	44.9								
8	147.2	147.2	149.4	23	205.6	210.8	211.2								
9	27.6	27.5	27.5	24	65.8	69.2	82.3								
10	29.4	29.3	29.2												
11	63.0	62.9	63.6												
12	47.3	47.3	48.9												
13	44.4	44.4	46.4												
14	46.1	46.1	50.9												
15	49.8	49.7	48.7												

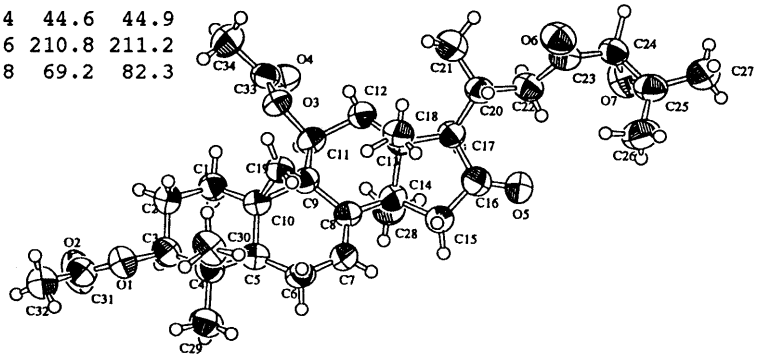


Fig.2. ORTEP Drawing of Diacetate of **4** (**5**) with Atomic Numbering

Cimicifugoside H-3 (**2**) has a trinor-triterpenic genin part ($C_{27}H_{40}O_5$) because the xyloside **2** has the molecular formula $C_{32}H_{48}O_9$. Structural similarity of **2** to **1** was shown by comparison of their ^{13}C-NMR spectral data (Table I), though

minor differences were observed between chemical shifts assignable to C-22,23 and 24. The reducing nature of **2** was demonstrated by a positive coloration (blue) with alkaline blue tetrazolium reagent: an α-ketol structure at C-23 and 24 is reasonably justified. We propose the structure 11β,24-dihydroxy-3β-(β-D-xylopyranosyloxy)-25,26,27-trinor-9,19-cyclolanost-7-ene-16,23-dione for **2**.

Cimicifugoside H-4 (**3**), positive to alkaline blue tetrazolium reagent, has the same molecular formula as **2**. On treatment with potassium hydroxide in methanol, **3** afforded an α-hydroxyenone {g in Fig.1, UV λmax (MeOH); 273nm (ε=18,800)}. Taking NOE and NOESY experiments into consideration, we propose the structure **3** shown in Chart 1. Its genin part, foetidinol, has recently been isolated from the rhizome of *Cimicifuga foetida*.[8] Thus, cimicifugoside H-4(**3**) is 3-*O*-xyloside of foetidinol.

Cimicifugoside H-1 has a parental structural feature for some of the 9,19-cyclolanostanes isolated so far from *Cimicifuga* plants. It is particular to the triterpenic genins of known *Cimicifuga* glycosides that the three cimicifugosides have a hydroxy group at C-11. The genin parts of cimicifugosides H-3 and H-4 are probably those resulting from loss of the three carbons from cimicifugoside H-1. A probable biogenetic route to cimicifugoside H-4 is an intramolecular aldol condensation between C-16 and C-24 of cimicifugoside H-3.

REFERENCES AND NOTES

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4) K.Baba, M.Kozawa, K.Hata, T.Ishida, M.Inoue, *Chem. Pharm. Bull.*, **29**, 2182 (1981).

5) Full characteristics will be presented in a full paper. a) **1**: $[\alpha]_D$ -43.5° (MeOH). *Anal.* Calcd. for $C_{35}H_{52}O_9$: C,68.15; H,8.50. Found: C,67.87; H,8.70. b) **2**: $[\alpha]_D$ -22.3° ($CHCl_3$-MeOH=1:1). HR-(+)-FABMS Calcd for $C_{32}H_{49}O_9$: 577.3377. Found: 577.3382. $(M+H)^+$ c) **3**: $[\alpha]_D$ -75.0° ($CHCl_3$-MeOH 1:1). (+)-FABMS m/z: 577. (-)-FABMS m/z: 575. HR-(+)-FABMS Calcd for $C_{32}H_{48}O_9Na$:599.3196. Found:599.3208. $(M+Na)^+$ d) **5**: $[\alpha]_D$ +10.1° ($CHCl_3$).

6) Y.Kawazoe, Y.Sato, M.Natsume, H.Hasegawa, T.Okamoto, K.Tsuda, *Chem. Pharm. Bull.*, **10**, 338 (1962).

7) X-Ray crystallographic analysis of **5** :$C_{34}H_{48}O_7$, prismatic crystals, space group $P2_12_12_1$ with a=13.582(3)Å, b=22.856(3)Å, c=10.292(3)Å, V=3194(1)Å^3, Z=4, Dc=1.182gcm^{-3}, R=0.056 for 2395 reflections.

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