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Hippuristerone A, a novel polyoxygenated steroid from the gorgonian *Isis hippuris*

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Abstract

A novel (22*R*,23*S*,24*S*)-polyoxygenated steroid, hippuristerone A (**1**), has been isolated from a Taiwanese gorgonian *Isis hippuris*. The structure of **1** was elucidated by 1D and 2D NMR and further confirmed by a single-crystal X-ray diffraction analysis.

Keywords: gorgonian; *Isis hippuris*; hippuristerone; polyoxygenated steroid.

Previous studies on the chemical constituents of the gorgonian corals of the genus *Isis* have led to the isolation of several interesting spiroketal steroids.[1–4] In this paper, we report the isolation and structure determination of a novel (22*R*,23*S*,24*S*)-polyoxygenated steroid, hippuristerone A (**1**), which contains independent substitution groups at all the side chain carbons (C20 and C22–C25).

Specimens of the gorgonians (wet wt, 3.0 kg), collected from the coral reef of Green Island, Taiwan in February 1999, were immersed successively in *n*-hexane and CH_2Cl_2. The combined crude extract was separated by Si gel column chromatography. Hippuristerone A (**1**) was obtained as colorless prisms.[5] The HRFABMS of **1** established a molecular formula of $C_{33}H_{52}O_7$ [$(M+Na)^+$ m/z 583.3609], implying eight degrees of unsaturation. The IR spectrum of **1** showed absorption bands for hydroxyl (ν_{max} 3352 cm^{-1}), ester carbonyl (ν_{max} 1726 cm^{-1}), ketone carbonyl (ν_{max} 1712 cm^{-1}) groups, and C–O stretching (ν_{max} 1252 cm^{-1}) in the molecule of **1**. Its ^{13}C NMR spectrum showed signals for carbons of one ketone (δ 211.8, s), two ester carbonyls (δ 171.4, s; 169.8, s), five carbons bonded to an oxygen (δ 85.6, s; 79.4, s; 77.2, d; 70.1, d; 67.4, s), two quaternary carbons (δ 43.1; 35.6), eight methine, eight methylene, and nine methyl carbons. In the ^1H NMR spectrum, two acetoxy methyl signals (δ 2.12, 3H, s; 1.98, 3H, s) were

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observed. Therefore, metabolite **1** must be a pentacyclic compound. By the assistance of 2D NMR spectra, including COSY, HMQC, and HMBC, **1** was shown to be a steroid. The protons of the hydroxy- and acetoxy-bearing methines which show signals at δ 4.03 (1H, dd, $J=8.0$, 8.0 Hz) and 4.63 (1H, d, $J=10.8$ Hz) were assigned to H-16 and H-22, respectively. The doublets at δ 0.90 (3H, d, $J=8.0$ Hz) and 0.86 (3H, d, $J=8.0$ Hz) were attributed to H_3-28 and H_3-29. Furthermore, the five singlets at δ 1.58 (3H), 1.55 (3H), 1.44 (3H), 1.02 (3H), and 0.96 (3H) were assigned to the resonances of H_3-21, H_3-26, H_3-27, H_3-19, and H_3-18, respectively. Based on the consideration of molecular formula, the second acetoxy group should be attached at C-25 and one more oxygen atom had to be placed between C-17 and C-20 to form a tetrasubstituted epoxide. The ketone functionality at C-3 was confirmed by its HMBC correlations to H_2-4 and H_2-2. Several ^{1}H–^{1}H COSY and HMBC correlations provided unambiguous evidence for the side chain (Fig. 1 and Table 1).

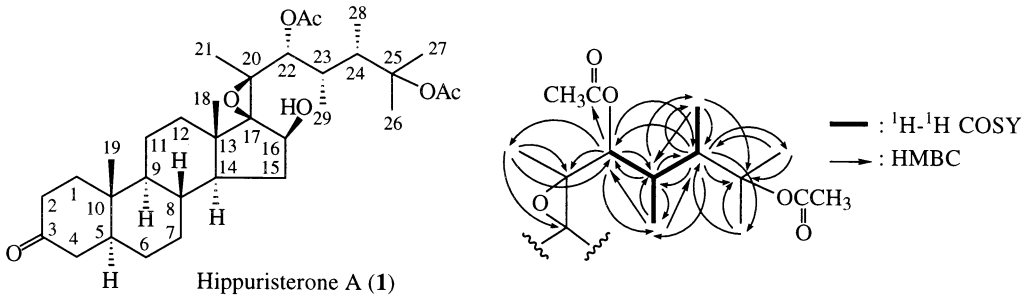

Figure 1. HMBC and ^{1}H–^{1}H COSY correlations of the side chain of **1**

Table 1
Selective ^{1}H–^{1}H COSY, HMBC, and NOESY correlations for **1**

C/H	^{1}H–^{1}H COSY	HMBC	NOESY
3		H-2α/β, H-4α/β	
16	H-15α/β	H-15β	H-14, OH-16, H-22, H-23, H-24
17		H_3-18, H_3-21	
20		H-16, H_3-21, H-22	
21		H-22	
22	H-23	H_3-21, H-23, H-24, H_3-29	H-16, OH-16, H-24
23	H-22, H-24, H_3-29	H-22, H-24, H_3-28, H_3-29	H-16
24	H-23, H_3-28	H-22, H-23, H_3-26, H_3-27, H_3-28, H_3-29	H-16, H-22
25		H-24, H_3-26, H_3-27, H_3-28	
26		H-24	
27		H-24	
28	H-24	H-23, H-24	
29	H-23	H-22, H-23, H-24	
22-O*C*OMe		H-22	

The relative stereochemistry of **1** was deduced using a NOESY spectrum (Fig. 2 and Table 1). In the NOESY spectrum of **1**, H_3-21 did not give correlation with H_3-18, and H-16 was found to exhibit correlations with H-14, H-22, H-23, and H-24. Thus, H-16 should be placed on the α phase. Detailed consideration of molecular models, suggested that compound **1** might be a

17β,20β-epoxy derivative and the side chain substituents of **1** should possess orientation of C-22α, C-23α, and C-24α. Thus, **1** is considered to be a novel 17β,20β-epoxy steroid possessing an unprecedented (22*R*,23*S*,24*S*)-23,24-dimethyl-22,25-diacetoxyl side chain in the molecule. A single-crystal X-ray structure analysis was carried out in order to confirm the molecular structure of **1**. The X-ray structure (Fig. 3) demonstrates the 17β,20β-epoxy functionality and the β-orientation of 16-OH. Also, the substituents and configurations at side chain carbons (C22–C25) were established unambiguously as represented in the molecular structure of **1**.[6]

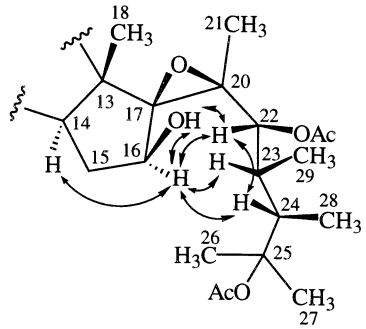

Figure 2. Selected NOE correlations of **1**

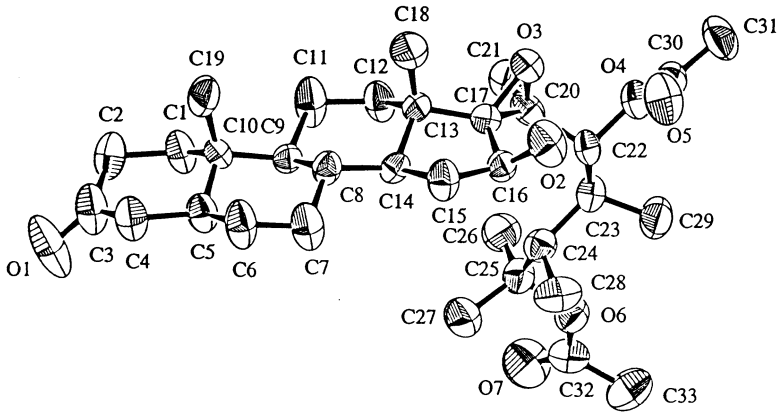

Figure 3. A computer-generated ORTEP plot of **1** showing the relative configuration. Hydrogen atoms have been omitted for clarity

Acknowledgements

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5. Hippuristerone A (**1**) was obtained as colorless prisms (14.2 mg), and eluted with *n*-hexane/EtOAc=4/1; mp 153–154°C; $[\alpha]_D^{25}$ +17° (*c* 0.5, $CHCl_3$); IR (KBr) ν_{max} 3352, 1726, 1712, and 1252 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.63 (1H, d, J=10.8 Hz, H-22), 4.03 (1H, dd, J=8.0, 8.0 Hz, H-16), 3.23 (1H, br s, OH-16), 2.35 (1H, ddd, J=15.0, 10.5, 7.0 Hz, H-2β), 2.33 (1H, m, H-2α), 2.31 (1H, m, H-4β), 2.25 (1H, m, H-23), 2.20 (1H, dd, J=8.0, 3.5 Hz, H-15α), 2.12 (3H, s, acetate methyl), 2.10 (1H, m, H-4α), 2.01 (1H, dd, J=5.0, 1.5 Hz, H-1α), 1.98 (3H, s, acetate methyl), 1.94 (1H, q, J=8.0 Hz, H-24), 1.81 (1H, m, H-12β), 1.62 (1H, m, H-11α), 1.59 (1H, m, H-8), 1.58 (3H, s, H_3-21), 1.55 (3H, s, H_3-26), 1.53 (1H, m, H-5), 1.47 (1H, m, H-12α), 1.44 (3H, s, H_3-27), 1.40 (1H, m, H-11β), 1.38 (1H, m, H-15β), 1.36 (1H, m, H-1β), 1.19 (1H, ddd, J=15.0, 8.0, 3.5 Hz, H-14), 1.02 (3H, s, H_3-19), 0.96 (3H, s, H_3-18), 0.90 (3H, d, J=8.0 Hz, H_3-28), 0.86 (3H, d, J=8.0 Hz, H_3-29), and 0.79 (1H, dt, J=8.4, 2.8 Hz, H-9); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 211.8 (s, C-3), 171.4 (s, acetate carbonyl), 169.8 (s, acetate carbonyl), 85.6 (s, C-25), 79.4 (s, C-17), 77.2 (d, CH-22), 70.1 (d, CH-16), 67.4 (s, C-20), 53.2 (d, CH-9), 48.4 (d, CH-14), 46.5 (d, CH-5), 44.6 (t, CH_2-4), 43.1 (s, C-13), 40.2 (d, CH-24), 38.4 (t, CH_2-1), 38.1 (t, CH_2-2), 36.3 (t, CH_2-12), 35.6 (s, C-10), 34.6 (d, CH-8), 33.5 (d, CH-23), 33.3 (t, CH_2-15), 31.4 (t, CH_2-7), 28.7 (t, CH_2-6), 25.1 (q, CH_3-27), 23.0 (q, CH_3-26), 22.6 (q, acetate methyl), 21.3 (t, CH_2-11), 21.0 (q, acetate methyl), 16.5 (q, CH_3-21), 15.5 (q, CH_3-18), 11.9 (q, CH_3-29), 11.4 (q, CH_3-19), and 10.4 (q, CH_3-28); FABMS m/z 583 [2 $(M+Na)^+$], 501 (0.7), 483 (2), 441 (2), 423 (2), 371 (3), 341 (6), 313 (5), and 43 (100); HRFABMS 583.3609 ($C_{33}H_{52}O_7Na$, calcd 583.3611).
6. Atomic coordinates for this structure have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.