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Two New Bis-tetrahydrofuran Ring Annonaceous Acetogenins from the Roots of *Uvaria calamistrata*

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Abstract: Two mild-cytotoxic bistetrahydrofuran (THF) ring annonaceous acetogenins named calamistrins F (**1**) and G (**2**) were isolated from the ethanolic extract of the roots of *U. calamistrata* Hance. Their structures including the relative and absolute configurations were determined by chemical derivation and spectral analysis. Calamistrins F and G were a pair of epimers at C-26 which both had THF ring from C-18 to C-25 and three OH groups at C-5, C-17 and C-26.

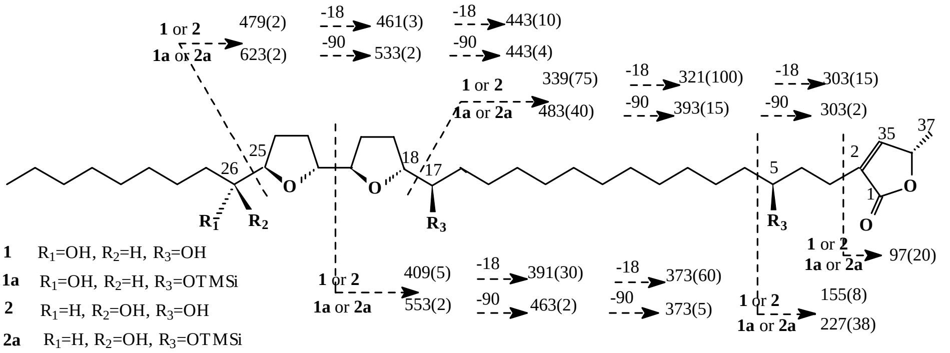
Keywords: Annonaceae, acetogenin, *Uvaria calamistrata*, calamistrin F, calamistrin G.

Although our research revealed that narumicin-II and desacetyluvaricin were the two major bioactive bis-THF ring acetogenins in the roots of *Uvaria calamistrata* Hance, two new bis-THF ring annonaceous acetogenins with mild-activities named calamistrins F (**1**) and G (**2**) had also been isolated. The acetogenins were trace constituents in the plant and structurally had the characteristics of OH-flanked THF ring from C-18 to C-25 and a third OH group at C-5.

1 was isolated as waxy solid. The FABMS of **1** gave [MH]+ peak at *m/z* 623, which, combining with elemental analysis, suggested a molecular formula $C_{37}H_{66}O_7$. The absorption band at 3427 cm^{-1} in the IR spectrum of **1** and the $[MH-3H_2O]^+$ ion peak at *m/z* 569 in the FABMS of **1** indicated the presence of three OH groups. The ^1H NMR signals at δ 7.04 (d, J=1.4 Hz, H-35), 5.01 (m, H-36), 3.59 (m, H-5), 2.44 (m, H-3a), 2.36 (m, H-3b) and 1.42 (d, J=5.7 Hz, H-37) and ^{13}C NMR signals at δ 173.80 (C-1), 149.41 (C-35), 134.10 (C-2), 77.53 (C-36), 70.69 (C-5), 21.51 (C-3) and 19.08 (C-37) indicated the existence of an α, β-unsaturated γ-lactone moiety with 5-OH group[1]. The ^1H NMR signals at δ 3.39 (2H, m, H-17, 26), 3.87 (2H, m, H-18, 25), 3.83 (2H, m, H-21, 22) and the ^{13}C NMR signals at δ 83.13 (2C, C-18, 25), 74.07 (2C, C-17, 26) and 81.72 (2C, C-21, 22) were typical signals of the adjacent bis-THF ring with flanking OH groups on both sides in acetogenins. These NMR data also suggested the existence of bis-THF ring and two OH-containing methines with *threo*-*trans*-*threo*-*trans*-*threo* relative configuration[1, 2]. The location of bis-THF ring from C-18 to C-25 and flanking OH groups at C-17 and C-26 in **1** was determined by the diagnostic fragment ion peaks in the EIMS of **1** and its TMSi derivative (**1a**) (see **Figure 1**).

The (*R*)- and (*S*)-MTPA esters (**1s**/**1r**) of **1** were used to determine the absolute configuration of carbinol chiral centers in **1**. Analysis of the difference between the chemical shifts of the diagnostic protons in **1** revealed that C-5, C-19 and C-26 all possessed *R* configurations. Based on the elucidated relative relationship, C-20, C-23, C-24 and C-25 also all possessed *R* configurations. The stereochemistry of C-36 was conveniently assigned to be *S* due to the fact that all acetogenins having been determined by various methods all prossessed *S* configuration at C-36.

Figure 1. The diagnostic fragment ions of **1**/**1a** and **2**/**2a** in EIMS



2 has the same molecular formula and similar ^{1}H and ^{13}C NMR spectra and EIMS fragmentation as **1**, which indicated that **2** is a bis-THF ring acetogenin with the same lactone moiety and the same location of three OH groups as **1**(see **Figure 1**). The existence of the adjacent bis-THF ring with a flanking OH group at both sides in **2** was indicated by the ^{1}H NMR signals at δ 3.39 (1H, m, H-17), 3.84 (4H, m, H-18, 21, 22, 25), 3.93 (1H, m, H-26) and the ^{13}C NMR resonances at δ 74.07 (C-17), 83.36 (C-18), 82.41 (C-21), 82.19 (C-22), 82.82 (C-25) and 71.52 (C-26), which also suggested the *threo-trans-threo-trans-erythro* relative configuration of this bis-THF ring region[2, 3]. Here, the *erythro* relative configuration between C-25 and C-26 was submitted to the consideration that all the *erythro* in acetogenins with *threo-trans-threo-trans-erythro* relative configuration were assigned for the far side of bis-THF ring from lactone moiety. The Mosher method determined the absolute configuration of **2** as 5*R*, 17*R*, 18*R*, 21*R*, 22*R*, 25*R*, 26*S* and 36*S*. **1** and **2** were a pair of epimers at C-26 mutually.

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